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OSTEOID OSTEOMA

With Case Reports

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OSTEOID osteoma is a benign bone lesion, so named by Jaffe (2) in 1935. He believes it to be a definite entity, and defined it as follows: "The lesion is a benign osteogenic tumor of slow growth. The original phase of its evolution in a given site seems to be the proliferation of the local bone-forming mesenchyme and particularly of its osteoblasts. Indeed, at an early stage, the tumor may consist largely of a vascular mesenchymal substratum, closely packed with osteoblasts, although showing also a scattering of osteoclasts." He (3) made a further contribution to the subject in 1936. In a later study of this condition in 33 patients by Jaffe and Lichtenstein (4), they saw no reason for changing Jaffe's original conception of the lesion.

Since the available literature on this subject is small, it is felt that a further discussion of the disease with a report of an additional 5 patients would be in order. Furthermore, it is believed that the condition is more prevalent and widespread than the literature indicates.

As stated, it was in 1935 that Jaffe described in detail for the first time this benign bone lesion, and reported 5 cases. All of these patients had come to his attention in the year 1933. Because of the similarity in symptomatology, physical and roentgenographic findings, and the pathologic pattern, he gave the lesion the name "osteoid osteoma."

In this same article Jaffe refers to a paper entitled "Sclerosing Osteomyelitis of Carpal Scaphoid," 1929, by Hitzrot, with roentgenograms similar to his Cases 1, 2, and 3, but with indefinite microscopic data. Again he refers to 2 case reports by Bergstrand, 1930, under the heading of "a peculiar and probably not hitherto described osteoblastic disease in long bones of hands and feet." Jaffe feels that these were probably osteoid osteomas. By 1940, Jaffe and Lichtenstein had studied material from 33 patients with osteoid osteoma. Kleinberg (5) reported a case of osteoid osteoma in 1941. Five more cases were reported by him (6) in 1943. Mallory reported 1 case in 1941. Horwitz reported 1 case in 1942. Thoma referred to the condition in 1938, and Lewis recently reported 11 cases, in 1 of which there was no microscopic confirmation, which we hold to be imperative before a final diagnosis is made. With our 5 cases, a total of 58 patients with osteoid osteoma have been studied.

ETIOLOGY

The etiology of the disease is unknown. Whether trauma is a factor in precipitating the condition has not been confirmed.

From the Willis C. Campbell Clinic.
Read before the Section of Pathology, Southern Medical Association, St. Louis, Missouri, November 14, 1944.

CLINICAL DATA

Age. The lesion is most commonly seen in the second and third decades of life; however, it has been reported in both younger and older individuals. Our youngest patient was 16 (Case 5), the oldest 40 years of age (Case 4).

Sex. In the 33 patients studied by Jaffe and Lichtenstein, there were 22 males and 11 females. In our series of 5 cases there are 4 males and 1 female.

Symptomatology. Pain is the dominant presenting complaint in all patients. Its intensity varies, being relatively mild to intense, and even preventing sleep in some patients. It may be intermittent in the early stages, gradually becoming more constant until it finally forces the patient to seek medical advice. The pain has usually been present for 3 or more months when the patient is first seen by his physician. The pain is most often localized to a very small area frequently not over 1 centimeter in diameter directly over the site of the pathology; occasionally it is referred (Cases 1, 4, and 5). The pain and tenderness may antedate any other clinical or even roentgenographic evidence of the disease by several weeks, or even months. The fact that the patient has local pain with few physical findings to support it, and even negative roentgenograms in some cases, is one of the most striking features of the disease.

Physical findings. Exquisite "finger point" tenderness over a small area, rarely more than 1 centimeter in diameter, is an almost constant finding. This one finding should immediately arouse suspicion in an astute observer that he may be dealing with a bone lesion of the variety, osteoid osteoma. The degree to which this physical sign is noted will, of course, vary according to whether the lesion is near to or more remotely placed from the surface of the body.

Swelling of the adjacent overlying soft tissue is present occasionally. This is due to congestion and edema of the adjacent periosteum (Cases 2 and 3). Local fever is very rare, and redness of the skin is seldom noted. Occasionally the patient will complain of a "knot" at the site of the lesion, which is due to a deposit of sclerotic reactive new bone beneath the periosteum. This is especially prone to occur if the lesion is in the shaft cortex of a long bone, and may easily obscure the real pathology unless overexposed roentgenograms are taken at different angles to bring out the nidus, as suggested by Pomeranz and quoted by Jaffe and Lichtenstein. Whether the patient will have a limp or dysfunction of a joint depends, of course, upon the location of the lesion.

Two of our patients (Cases 3 and 4) gave a history of direct trauma, 7 months and 24 months, respectively, before admission to the Clinic.

Skeletal sites. Osteoid osteomas have been found in the following bones: namely, tibia, fibula, femur, vertebra, humerus, ulna, skull, facial bone, phalanges (manual and pedal), patella, calcaneus, talus, tarsal navicular, and ilium. The bones involved in our 5 cases were as follows: second cervical vertebra (1); humerus (1); tibia (2); and talus (1).

Roentgenographic findings. The x-ray film of the affected region will almost always reveal a bone lesion responsible for the symptoms and signs presented by the patient. Occasionally the first picture may be negative or the lesion may be so minute that it cannot be seen even after as long as 3 months from the onset of pain, as in the case of 1 of our patients (Case 2). Therefore, the age and location of the lesion will determine to some degree its roentgenographic characteristics. A typical picture of an osteoid osteoma (Case 3) reveals an oval to round area from a few millimeters to 1 or 2 centimeters in its greatest diameter, the center of which presents small areas of rarefaction and condensation. Surrounding this is a narrow zone of condensation and, in turn, just outside of this is a zone of rarefaction. The surrounding parent bone is, as a rule, sclerosed for a variable depth. Varying degrees of this roentgenographic description will be noted; for example, (a), our Case 2, presented no bone defect in the first x-ray picture, but weeks later a very small nidus showed up in the external condyle of the humerus; example (b), in our Case 4, a small lesion incorporated in a very dense, thickened, sclerosed tibia was obscured by the thick sclerotic bone. This may be easily overlooked in a routine roentgenogram. In the latter

case, one may have to make several overexposed films at different angles before the lesion, which may not be over 3 or 4 millimeters in size, can be seen.

Osteoid osteoma may occur in the cortex just beneath the periosteum (Case 1), intracortically (Case 4), or in spongy bone (Case 2). Evidence thus far supports the theory that a much greater defensive response to the lesion is made in the form of marked thickening and condensation of the cortex subperiosteally and intramedullarly if the lesion is situated intracortically in the shaft of a long bone, than if it is located in cancellous bone. The reason for this, perhaps, may be due to the presence of larger stores of calcium, and the factors essential to its regimentation being more potent in cortical bone than in spongy bone. However, this is purely theoretical and based on conjecture. We have no evidence that this benign bone lesion has ever invaded or broken through the periosteum, but, if incompletely removed surgically, it will continue to grow and produce pain as it did before operation. Osteoid osteoma has never been known to metastasize.

Laboratory findings. All laboratory tests in our cases, including Wassermann, blood counts, urinalyses, and bacteriologic cultures, were nonrevealing as to the nature of the lesions. Cultures were made in 2 of our patients (Cases 1 and 3).

PATHOLOGY

If the pathologic lesion is near or on the surface of cortical bone, the periosteum will likely be thickened, edematous, and show capillary engorgement (Case 1). The involved portion of the cortex will also be hemorrhagic in appearance. If, on the other hand, the nidus is within the dense shaft cortex, one may find much sclerotic new bone having been laid down beneath the periosteum as well as on the medullary side of the bone. The gross appearance of a typical osteoid osteoma usually consists of blood-stained, gritty, friable, cancellus-like bone. The cut surface shows reddish brown flecks mixed with pearl gray osteoid. The reddish brown flecks represent the calcified osteoid quite similar to callus, and the pearl gray the osteoid.

Microscopically, a typical picture of an osteoid osteoma (Case 3) consists of much vascular, richly cellular, embryonal type of osteogenetic connective tissue representing all elements necessary in the development of membranous bone from the most primitive myxomatous connective tissue cell to fibrous connective tissue cell, and finally to the osteoblast, in which are islands and trabeculae of osteoid, calcified osteoid, and atypical ossified bone surrounded by large numbers of osteoblasts and not a few osteoclasts. At most any place in the vascular cellular stroma, one may see osteoblasts and an occasional osteoclast. Osteoclasts, if adjacent to calcifying osteoid or atypical bone, usually lie in little depressions called Howship's bays.

The foregoing is a description of the center of the lesion, but as the periphery is approached there is more of the osteoid and calcified osteoid, which is responsible for the sclerotic outer zone seen in the roentgenogram. Just outside of this zone and separating it from the more or less sclerotic parent bone, the primitive vascular mesenchymal type of connective tissue predominates, with its ramifications extending into and filling the already enlarged adjacent interstices of the perifocal sclerosed bone. This tissue may reveal osteoblasts, but no osteoid or calcified osteoid, and is believed to be the precursor to the formation of the pathologic lesion.

DIAGNOSIS

The diagnosis is relatively easily made provided the pathologic process has developed to the point where there is roentgenographic evidence to support the clinical findings, and the physician is aware of the possibility of the presence of an osteoid osteoma and has been schooled in the symptomatology, physical findings, and roentgenographic evidence produced by the pathologic process. In summarizing, the following are the important features which are of aid in making the diagnosis:

1. Pain of a dull, aching character, most annoying at night.

2. Pain localized, for the most part, to a small area, but which may be referred (Cases 1, 4, and 5).

3. Tenderness directly over the site of the lesion, and usually confined to a small area 1 or 2 centimeters in diameter.

4. Soft tissue swelling may or may not be present (Cases 2 and 3).

5. Bony tumefaction, especially if the lesion is in the shaft cortex of a long bone (Case 4).

6. Local fever and redness are very rare.

7. No noteworthy systemic symptoms have been observed.

8. All routine laboratory tests, including culture of the lesion, are negative.

9. The majority of the patients are in the second or third decades of life when first seen.

If one is not experienced in the symptoms and physical findings produced by this disease, and especially the roentgenographic features, he may easily overlook the lesion. Furthermore, he will be prone to misinterpret it as one of an inflammatory nature. This has been a common error committed by those unacquainted with the disease. Of all the diagnostic criteria, the sharply localized pain and the roentgenographic picture, which appears to be pathognomonic in many cases, are the most important.

Differential diagnosis. Osteoid osteoma must be differentiated from (1) sclerosing nonsuppurative osteomyelitis of Garré, (2) Brodie's intracortical bone abscess, (3) osteogenic sarcoma, and (4) Ewing's endothelial myeloma.

An osteoid osteoma of the shaft cortex of a long bone, such as the tibia, has been wrongly diagnosed as sclerosing nonsuppurative osteomyelitis. One of our cases (Case 4, Fig. 10) is a typical example of this error by both the clinician and the pathologist. It was only through a critical examination of the greatly thickened, surgically removed cortical slab of bone by serial X-ray films with different exposure intensities, by Colonel de Lorimier of the Army School of Roentgenology of Memphis, that the small nidus representing the osteoid osteoma was found. A preparation was then made which revealed, microscopically, osteoid osteoma. The microscopic section was poor, due to marked desiccation as a result of the specimen having remained out of fixative solution for a long time.

Microscopically, osteoid osteoma may be differentiated from osteomyelitis of Garré and Brodie's abscess because of the absence of an inflammatory cellular reaction and by the presence of the typical tumor tissue.

There is little to support misinterpretation of osteoid osteoma as an osteoblastic osteogenic sarcoma, but to one unfamiliar with its microscopic picture consisting of much embryonal, osteogenetic connective tissue, marked osteoblastosis, osteoid, calcified osteoid, and atypical osseous tissue, there is some ground for such an error. Roentgenographic findings usually render valuable aid in avoiding such an error. The only reason for mentioning Ewing's tumor is because of the similarity in the early sclerosis produced by both pathologic processes as revealed roentgenographically, especially when Ewing's tumor appears beneath the periosteum of the shaft cortex of a long bone. Of course, the microscopic evidence is decisive.

PROGNOSIS

The prognosis is uniformly good provided all of the lesion is excised. On the contrary, if it is not removed completely, pain will continue or recur, as the case may be. The prognosis, therefore, depends upon accurate diagnosis and localization of the lesion, and complete extirpation of it.

TREATMENT

Surgical excision of the pathologic lesion is the treatment of choice provided the area is accessible to surgery. Moreover, it is the only treatment which has hitherto been tried and described in the literature. So far as is known, no other treatment, such as deep roentgentherapy, has ever been tried. As the latter seems to have little or no effect upon the primitive malignant mesenchyme of osteogenic sarcoma, one may assume that it would have little if any effect on osteoid osteoma which, microscopically, at least, is not far removed from osteogenic sarcoma.

CASE REPORTS

CASE 1. E. C., No. 47890, white, male, aged 2[illegible] years, was admitted to the clinic on November 2[illegible] 1939, with pain in the right leg from the knee dow[illegible] and a tender spot over the medial surface of the tibi[illegible]

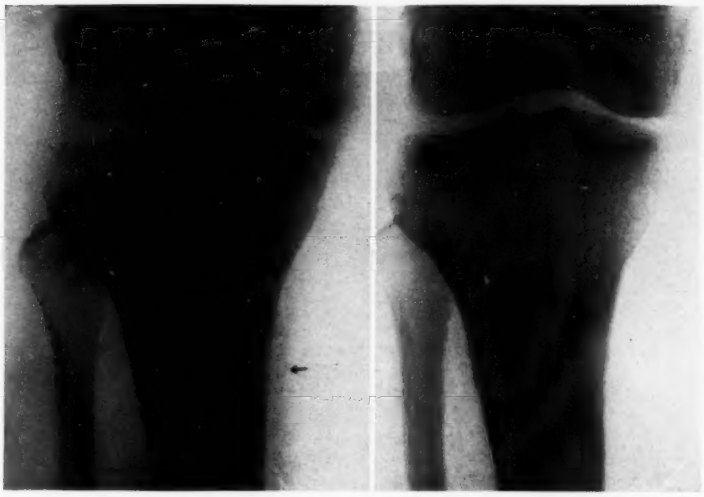

Fig. 1, left. Case 1, No. 47890. Anteroposterior roentgenogram, November 2, 1939, of right knee shows a rarefied area (10 by 2 mm.) on the medial surface of the tibia just beneath the periosteum as indicated by arrow.

Fig. 4. Case 1, No. 47890. Anteroposterior roentgenogram, March 16, 1942, shows old window made at the time of biopsy.

just below the knee. Onset was 3 months ago; the leg became sore following a softball game. Soreness has continued, especially at night. Pain awakens him at night. The pain has remained about the same.

Upon examination the right knee revealed normal contour and there was no limp. A tender point was present over the anteromedial aspect of the right tibia just below the condyle. Pressure over the tender area and flexion to 50 degrees produced severe pain in affected part. There was no tumefaction.

On November 2, 1939, roentgenogram of the right knee (Fig. 1) was negative except for a small, rarefied area in the cortex, anteroposterior view, 6.5 centimeters below the articular surface of the medial tibial condyle.

On the same day, the tibia was explored at the painful site. The periosteum was found to be somewhat thickened and congested. Beneath this was a reddish area in the cortex of the tibia about 1 centimeter in diameter. A window of bone 2 by 1 inches in diameter including the diseased area was removed.

Gross pathologic examination revealed a flat piece of cortical bone measuring 4 by 2 centimeters, in the center of which was a small, dark, hemorrhagic spot 2 millimeters in diameter. A small amount of cancellous bone was attached to the cortex. Microscopically, the section consisted of typical vascular preosseous connective tissue, osteoid and calcified osteoid trabeculae (Fig. 3, frontispiece). These were lined by many osteoblasts. A few osteoclasts were present about some of the trabeculae, lying in Howship's bays and also in the cellular stroma. Compact bone was on either side of the pathologic lesion. Between it and the lesion, and extending for some distance into the interstices of the parent bone, the osteogenetic type of connective tissue was seen to predominate. It appeared to be the precursor to the formation of the centrally placed lesion. The diagnosis by the author then was reactive new bone, but the lesion was now classified as an osteoid osteoma.

The immediate postoperative course was uneventful. The pain experienced before operation subsided, and he was allowed to resume work as a grocery clerk 5 weeks after operation. He was next seen on October 31, 1941, 2 years after operation, following his discharge from the Army because of recurrence of pain and soreness about the old lesion after drilling and strenuous exercise. Examination at this time revealed slight sensitiveness over the old scar with slight roughening of the tibial surface. There were no sensitive spots. On his last visit, March 16, 1942, there was generalized aching and slight swelling in the right leg about the old scar, and aching down the leg. This came on after he was on his feet for half an hour. Otherwise, the physical examination and roentgenographic films (Fig. 4) were negative. Some doubt arose as to the degree of pain the patient had, and its cause. Exploration of the leg was thought unjustified at that time. We have been unable to obtain a later follow-up on this case.

CASE 2. G. R., No. 54744, white, male, aged 34 years, was first seen in the Clinic on November 28, 1941, with pain and soreness in the right elbow of 3 months' duration. Exercise, such as playing tennis, aggravated the symptoms. He was awakened by the

Fig. 5, left. Case 2, No. 54744. Anteroposterior roentgenogram, November 28, 1941, of right elbow read as negative.

Fig. 6. Case 2, No. 54744. Anteroposterior roentgenogram March 19, 1942, 15 weeks after film in Fig. 5 was made reveals a small oval nidus with a condensed center surrounded by narrow rarefied zone in the external condyle of the humerus as indicated by arrow.

pain at night occasionally. There had been no swelling or redness, and no definite history of injury.

Examination of the elbow revealed a small area of "finger point" exquisite tenderness, and a visible and palpable fullness over the external condyle of the humerus between the epicondyle and olecranon process. The swelling had the consistency of soft tissue with slight fluctuation; no local fever. Range of motion in elbow was normal, but on extremes of motion pain was precipitated at the site of tenderness. Roentgenogram of the right elbow was negative (Fig. 5).

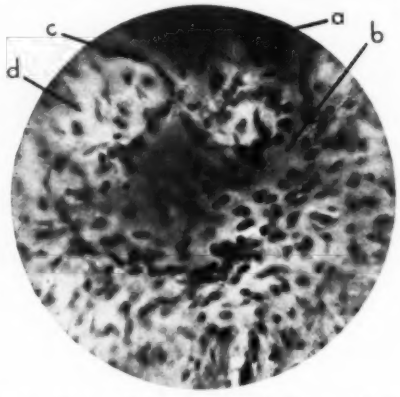

Fig. 7. Case 2, No. 54744. Photomicrograph, ×358, reveals calcified osteoid *a* and osteoid *b* surrounded by a layer of osteoblasts *c* and the cellular osteogenic connective tissue *d*.

Physical therapy to the elbow for a possible traumatic or infectious arthritis and omission of strenuous exercise were advised. He was next seen on March 19, 1942, (4½ months later) with the same symptoms and physical findings as on the first examination.

Roentgenogram (Fig. 6) made at this time revealed a small oval area of condensation surrounded by a rarefied zone measuring 6 by 7 millimeters in the external condyle of the humerus, 8 millimeters proximal to the articular surface.

The painful area was explored on April 14, 1942, and a 2 by 3 centimeter area of the external condyle was removed. The surgeon suggested the possibility of osteoid osteoma at the time of operation.

Grossly, in the center of the smooth, flat piece of thin cortical and cancellous bone 2 by 3 centimeters in size, there was a small, soft, dark reddish, discolored area. The microscopic section revealed a vascular, highly cellular structure in which there was much osteoid and calcified osteoid, forming a kind of lattice-work (Fig. 7, frontispiece). There were numerous osteoblasts bordering the trabeculae of osteoid and calcified osteoid, as well as in the cellular soft tissue. Osteoclasts were likewise common. The cellular soft tissue was composed of an embryonal preosseous type of osteogenetic fibrous connective tissue in which were seen numerous osteoblasts and a few osteoclasts. A few lymphocytes and plasma cells were seen in the soft tissue also. As in practically all of the cases, the cellular connective tissue seemed to separate, for the most part, the more centrally located osteoid and calcified osteoid material from the surrounding parent bone.

The patient's postoperative course was uneventful. The pain disappeared, but there was slight swelling and slight limitation of motion in the elbow when he was last seen about 30 days after operation.

Case 3. F. M., No. 60358, white, female, aged 40 years, was admitted to the clinic on July 22, 1943, with a painful, swollen right ankle since December, 1942, when a piece of wood had struck her over the anterior surface of the ankle. She experienced marked pain and swelling immediately, which had gradually increased to this time. She had not stopped walking, although the more she walked the more pain and swelling she had in the foot and ankle.

On examination there was found marked swelling and pitting edema of the ankle and foot. Marked tenderness all over the ankle, but especially over the anterior surface. There was no local fever, but the skin over the ankle was red. Motion in the ankle and joints of the foot was limited by marked pain.

A lateral roentgenogram of the ankle (Fig. 8a) revealed a peculiar circular lesion in the superior por-

Fig. 8a.

Fig. 8b.

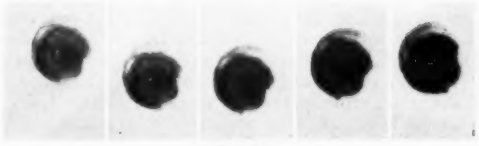

Fig. 8c.

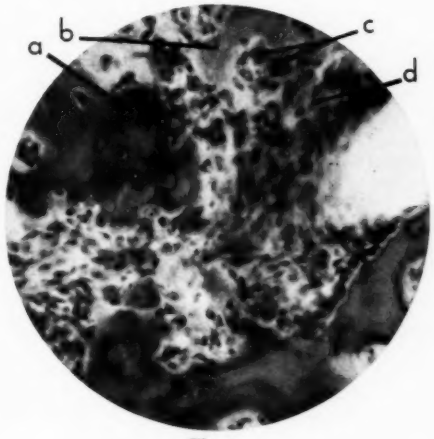

Fig. 9a.

Fig. 8d.

Fig. 8. Case 3, No. 60358. a, Lateral roentgenogram July 22, 1943, of right ankle shows a peculiar circular lesion of the neck of the talus, with about one-third of it protruding above the surface of the bone. It measured 9 by 9 millimeters. The center was radiolucent, and its periphery more sclerotic (zone 1.5 millimeters thick). Just outside of this sclerotic zone was a rarefied zone or halo. Since the lesion was not recognized as an osteoid osteoma, the patient was fitted with an ankle corset and she was allowed to return home for 3 weeks. On her return 3 weeks later, August 12, 1943, there was less swelling, but tenderness was still present over the anterior part of the talus. She was walking on the foot. She was next seen on 9 by 9 millimeters in the superior portion of the neck of the talus. About 1/3 of it protrudes above the cortex. The center is radiolucent while the margin is sclerotic and this in turn surrounded by another area of radiolucency. b, Lateral roentgenogram 8 months later, March 30, 1944, of right ankle shows the lesion to have grown to size 14 by 14 millimeters. c, Surgical specimen with small rim of perifocal bone showing varying degrees of intensity of exposure roentgenographically. d, Postoperative roentgenogram, April 14, 1944, shows the nidus to have been removed, leaving a rarefied area in the neck of the talus.

Fig. 9a. Case 3, No. 60358. Photomicrograph (×390) shows *a* calcified osteoid, *b* osteoid, *c* osteoclasts, *d* vascular osteogenic type of connective tissue.

Fig. 10. Case 4, No. 61666. Anteroposterior and lateral roentgenograms of left leg show marked sclerosis and thickening of the tibial cortex on both the periosteal and medullary aspects. No other pathology was seen.

March 30, 1944, 8 months after the first admission, at which time there was more swelling over the anterior part of the ankle and exquisite tenderness over the neck of the talus, with redness and increased local skin temperature. Another lateral roentgenogram (Fig. 8b) of the ankle showed the same lesion as was seen in the first film 8 months previously, except that it had grown larger, measuring 14 by 14 millimeters in diameter.

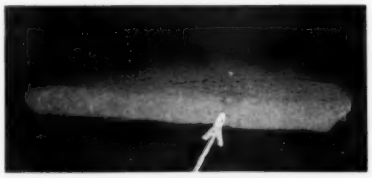

Fig. 11. Case 4, No. 61666. Roentgenogram of the surgical specimen shows the sclerotic bone with the small osteoid osteoma as indicated by arrow.

The tumor was removed surgically on April 4, 1944 (Fig. 8c). The tumor shelled out of its bed easily, leaving a smooth wall of spongy bone (Fig. 8d).

The specimen consisted of a spherical mass of dark red bone with about the consistency of callus, the surface of which was smooth except in the equitorial plane, where there was a shelf-like ledge of firm bone about 2 millimeters wide, a portion of the perifocal parent bone which had been removed with the tumor. The tumor proper measured 18 by 15 millimeters, and with the ledge, 18 by 17 millimeters. A microscopic section (Fig. 9, frontispiece) made through the equitorial plane of the tumor showed huge amounts of calcified osteoid and atypical bone occupying the center, with much osteoid nearer the periphery. The osteoblasts and osteoclasts were so numerous in the intertrabecular spaces that there was less vascular preosseous connective tissue than is usually seen; however, the latter was more plentiful where it seemed to separate, at least in part, the tumor from the perifocal bone. Parallel rows of osteoid separated by rows of osteoblasts were seen about the periphery of the tumor.

The patient made an uneventful recovery following removal of the tumor.

Case 4. L. P., No. 61666, white, male, aged 16 years, was first seen on November 23, 1943, with the history that, while chopping wood 2 years previously, a piece struck him across the anterior surface of the left leg above the ankle. He had pain for a short time. He had no further trouble until last winter, when he began to have pain in the injured area, soon followed by a small "knot" which had gradually increased in size. Pain had increased, too, whether on or off the leg. Leg ached at night some, and pain radiated into his ankle.

Examination revealed a hard, tender, oval swelling over the anteromedial aspect of the middle third of the left leg 3½ inches long and 1 inch wide. There was no local fever.

Roentgenograms (Figs. 10 and 14) showed marked sclerosis and thickening of the cortex on both the periosteal and medullary aspects. The pathologic defect within the sclerotic bone was not seen because of its dimness until on retrospect, after Colonel de

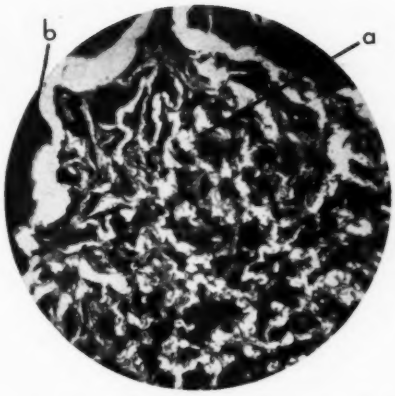

Fig. 12. Case 4, No. 61666. Photomicrograph (42×) shows osteoid osteoma *a* and a small rim of compact sclerotic bone *b*. The histopathologic detail was lost due to dehydration accounting for the vacuolated appearance of the nidus.

Lorimier of the Army School of Roentgenology, X-rayed the specimen with different degrees of exposure, a very small rarefied area was seen (Fig. 11).

A large window was made in the tibia on November 24, 1943. The overlying periosteum was found to be edematous and thickened, beneath which was much hard, sclerotic bone.

In the laboratory the nidus was overlooked in the gross description, which consisted of a greatly thickened, hard slab of cortical bone measuring 44 millimeters long by 12 millimeters wide by 15 millimeters thick, until after the X-ray film of the specimen had revealed the rarefied spot. A section was made through this defect which revealed tissue reaction to support the diagnosis of osteoid osteoma (Fig. 12), even though the tissue had become desiccated before the block was taken.

Recovery was uneventful; operation relieved the pain immediately. He was last seen June 7, 1944.

Case 5. J. T. S., No. 62586, white, male, aged 19 years, came to the Clinic on March 6, 1944, with pain in the cervical spine and referred pain to the left shoulder of about 1 year's duration. Pain has gradually increased in severity. There was no history of injury. He had been told he had a fracture, and wore a leather collar for 8 months without benefit.

Examination revealed the head being held tilted to the left, with considerable muscle spasm and tenderness just to the left of the upper cervical spinous processes and about an inch below the tip of the mastoid. Neck motion was limited to about 25 per cent of normal in all directions due to pain in the region of the second cervical vertebra. The left shoulder was negative.

Roentgenograms of the cervical spine (Fig. 14) revealed an oval lesion 20 by 18 millimeters in diameter of the left pedicle and adjacent parts of the second cervical vertebra. The center of the lesion

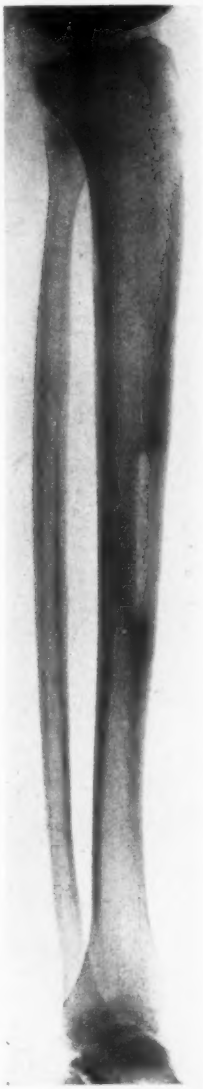

Fig. 13. Case 4, No. 61666. Roentgenogram, February 10, 1944, shows defect site of original thickened cortex.

was composed of rarefied and sclerotic areas which, in turn, were surrounded by a rarefied halo with a fuzzy margin. The adjacent portion of the spinous process was sclerotic.

The patient was referred to a neurosurgeon for biopsy for a possible osteogenic sarcoma. The biopsy was performed on March 9, 1944.

Fig. 14. Case 5, No. 62586. Lateral roentgenogram, March 6, 1944, shows a peculiar oval lesion (20 by 18 millimeters) of the pedicle arch of the second cervical vertebra. The center is sclerotic and is separated from the perifocal bone by a rarefied halo-like zone.

Our laboratory received only a part of the specimen, consisting of a small piece of soft, friable, bloodstained tissue measuring 10 by 10 by 3 millimeters, with one small, firm, cartilage-like nodule 2 by 2 millimeters in diameter attached. Microscopically, the section was typical for osteoid osteoma, with vascular osteogenetic connective tissue, osteoid, calcified osteoid, osteoblasts and osteoclasts (Fig. 15, frontispiece).

The patient was discharged to his home on the 13th postoperative day. While in the hospital he continued to receive analgesics for pain. The pain has persisted since he left the hospital, and just recently we learned that the patient is to return for further observation and treatment.

CONCLUSIONS

A discussion of osteoid osteoma, a relatively recently recognized disease entity of bone, is considered to be in order, as it is felt that it is, perhaps, frequently overlooked or erroneously diagnosed. We have misinterpreted the condition both clinically and histopathologically.

Its diagnosis in the hands of the inexperienced is most frequently confused with sclerosing nonsuppurative osteomyelitis of Garré, Brodie's bone abscess, and osteogenic sarcoma.

Diagnosis is relatively easy for one who is acquainted with the symptomatology, physical, roentgenographic findings and histopathology.

The frequency of this disease is, likely, much more prevalent than the literature on the subject may lead one to believe.

The age of the patient, predominantly in the second and third decades of life, and the persistent mild to severe localized pain with exquisite "finger point" tenderness, should arouse one to suspect the presence of osteoid osteoma.

If the nidus has developed sufficiently, the roentgenographic picture may be almost pathognomonic of osteoid osteoma. On the contrary, the roentgenogram may be negative even though symptoms may have been present for months. This type of case should be restudied roentgenographically at a later date, thus giving more time for the lesion to develop.

Physiologic response to the pathologic process varies materially as to whether it is located in spongy bone (Case 2, Figs. 5 and 6) or in the shaft cortex of a long bone (Case 4, Fig. 13).

The 5 cases of osteoid osteoma herein reported are presented not with the idea of contributing anything new to the subject, but mainly to try to popularize further and to spread the information already known regarding the disease. In this way it is hoped that the disease may be more readily and correctly diagnosed, and appropriate curative treatment applied when possible, which is, at this time, purely surgical.

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BACTERIOLOGICAL STUDIES OF CLOSTRIDIUM WELCHII INFECTIONS IN MAN

With Special Reference to the Use of Direct Smears for Rapid Diagnosis

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IN the years since Wilsdon's work, 1931, on the classification of Clostridium welchii much has been published on the toxins of this clostridium but the amount of work dealing with other aspects is comparatively small.

The intensive work on Clostridium welchii toxins must ultimately prove of great value for the understanding of infections in man, and has already provided the basis of tests for the rapid identification of the Clostridium welchii (Petrie and Steabben, 1943; Hayward, 1943; McClean et al., 1943). But its very importance has obscured the necessity for the study of other characteristics of the organism.

Investigations undertaken in this laboratory in a very large number of abortional infections and recently in a small series of postoperative and posttraumatic cases have shown that the capacity of the Clostridium welchii to invade the tissues rapidly is closely correlated with characteristics other than toxigenicity. Consideration of morphology, cultural characteristics etc., has led to a better understanding of certain aspects of Clostridium welchii infections and to the development of rapid diagnostic methods.

THE DETECTION OF CLOSTRIDIUM WELCHII BY THE DEMONSTRATION OF CAPSULES

Although the Clostridium welchii is universally recognized as a capsulated bacterium, comparatively little use has been made of this property for rapid identification.

Staining for capsules as a means of identification may be applied to smears from cultures and to smears made directly from material suspected of harboring Clostridium welchii. In this laboratory we have found Richard Muir's method highly satisfactory. The Indian ink method and others which merely demonstrate an unstained halo around the bacilli are not recommended, as such methods do not indicate variation in the structure of the capsule.

Whether or not strains of Clostridium welchii appear capsulated in culture depends very largely on the nature of the medium. In Wright's broth containing minced veal, less than 40 per cent of the Clostridium welchii strains isolated from the vagina are well capsulated, but if a small amount of serum or blood is present in the medium, approximately 90 per cent of the strains are sufficiently heavily capsulated to be provisionally identified. In our experience broths made from liver and those containing liver extract or bile are less satisfactory for demonstrating capsules than is Wright's broth.

The presence in the broth culture of other bacteria, whether aerobic or anaerobic, does not prevent the formation of capsules by Clostridia welchii. If the strain is distinctly capsulated, very small numbers of bacilli can be detected.

In this laboratory this method has given very few false positive results. Smears of more than 1,000 primary broth cultures have shown capsulated bacilli resembling the Clostridium welchii and 99 per cent of these cultures were proved to contain this organism. Aerobic spore-bearing bacilli may occasionally resemble slightly capsulated Clostridia welchii, but the frequency of formation of long chains by such aerobes, the presence of many spores, and the usually granular and faint staining of the aerobic bacilli reduce this source of error to negligible proportions.

Very occasionally heavily capsulated strains of the Bacillus coli may be mistaken for the

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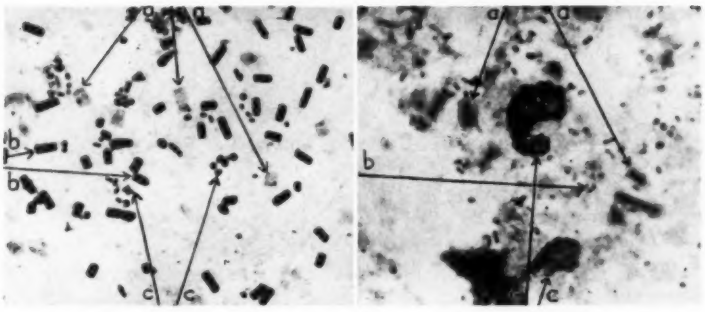

Fig. 1, left. Smear from broth culture showing capsulated Clostridia welchii in which the capsule completely obscures the bacterial rod so that the organism appears as a faintly stained cylinder or rectangle, *a*. Uncapsulated Clostridia welchii, *b*, and cocci, *c*, are also present. Muir's capsule stain. ×880.

Fig. 2. Cervical smear from severe abortional infection showing capsulated Clostridia welchii, *a*, in the presence of many cocci, *b*. Remnants of leucocytes, *c*, are also present. In this preparation the Clostridia welchii are larger than those usually seen in direct smears. Muir's capsule stain. ×880.

Clostridium welchii since in smears made from cultures containing blood or serum capsulated Bacillus coli sometimes retain the Gram stain, and with Muir's method the capsules of both these bacteria stain similarly.

Theoretically the Clostridium butyricum, the only other known capsulated clostridium, could be another source of error. This is of no moment in abortional infections, but in cultures from wounds, where contamination with the Clostridium butyricum is sometimes common (see MacLennan, 1943), this possibility should be borne in mind.

The appearance of the capsulated Clostridium welchii produced in broth varies. Usually a deeply stained rod is completely or partially surrounded by less deeply stained capsular material but forms in which the capsule obscures the bacterial rod may also be present. The latter are very faintly stained and appear as pale blue rectangles or cylinders (Fig. 1).

In our experience, the demonstration of capsulated rods resembling the Clostridium welchii in smears from broth cultures has proved as reliable for rapid diagnosis as the methods which depend on toxin production. In addition, it has been found that the former method has the advantages that the medium need not be freshly prepared and when inoculated does not require incubation in the anaerobic jar.

The methods suggested by McClean and associates for detecting in wound exudates the hyalurodinases and other specific exotoxins of the clostridia would be more rapid than cultural methods, but as yet there is no report of their extensive trial in human infections and they suffer from the disadvantage that they are comparatively complex and call for an experienced technical staff.

The simplest method for the rapid detection of the Clostridium welchii is the demonstration of typical capsulated Gram positive rods in smears made direct from the wound or any other site suspected of infection. Not only is it the most rapid method but it calls for the very minimum of equipment and is particularly suited for the routine examination of large numbers of cases in which an attempt is being made to detect the presence of the Clostridium welchii before the development of clinically recognizable infection.

Typical capsulated Clostridia welchii as seen in direct smears are shown in Figures 2 to 4.

Among the hundreds of specimens examined in the last 5 years in this laboratory, there was only one instance in which capsulated rods resembling Clostridia welchii were reported as present in direct smears when cultures from the same material failed to yield this organism. This discrepancy was probably due to the presence of a heavily capsulated strain of the Bacillus coli.

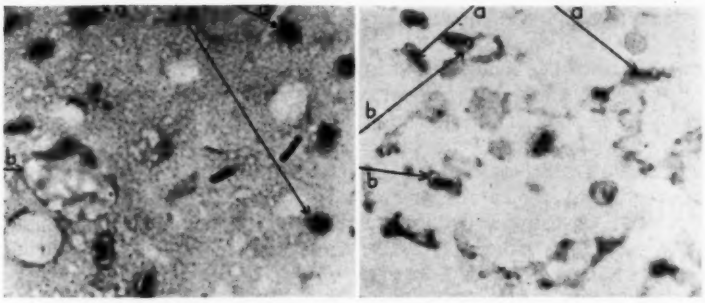

Fig. 3, left. Cervical smear from fatal abortional infection characterized by blood destruction. Most of the Clostridia welchii are short and stout with large but very fragile capsules, *a*. Portion of a leucocyte is present, *b*. Muir's capsule stain. ×880.
Fig. 4. Cervical smear from fatal abortional infection characterized by collapse. The Clostridia welchii tend to be long and thin, *a*, and the capsules have a clearly defined outline, *b*. Muir's capsule stain. ×880.

While the use of direct smears is practically never responsible for false positive results, it does not detect strains which fail to produce stainable capsules when growing in the tissues or discharges from the infected area, but, as will be shown in the next section, such strains are usually not important in human disease. Some of the strains which are not capsulated in direct smears produce recognizable capsules when growing in suitable broths.

THE EXAMINATION OF DIRECT SMEARS AS A MEANS OF DETERMINING THE SIGNIFICANCE OF THE PRESENCE OF THE CLOSTRIDIUM WELCHII

In man the mere detection of Clostridium welchii in a wound or other potential site of infection is not of great significance. It has long been known that this organism may be present without giving rise to clinically recognizable infection.

Infections following abortion. The chief bacteriological problem in abortional Clostridium welchii infection is the early diagnosis of the severe generalized infections. It has been apparent throughout the 5 years' investigation in this hospital that the recovery of the Clostridium welchii, be it from the genital tract, the urine, the peritoneal cavity or the blood, does not decide whether a severe infection exists or not. The study of smears from the cervical canal, however, has provided a solution of this problem (2, 3).

The significance of heavily capsulated Clostridium welchii. An investigation of 40 severe Clostridium welchii infections, including 32 in which this infection was the cause of death, showed that in every case whether characterized clinically by blood destruction or by collapse, heavily or very heavily capsulated bacilli could be demonstrated in smears from the cervical canal. In addition these smears showed evidence of destruction of the leucocytes. Recognition of the damage to the leucocytes was found to be particularly important. While the infection was still early, not all the leucocytes were damaged, whereas in the late stage of most of the untreated cases nothing but fragments of destroyed cells were seen. In the early stage of a severe infection there were always many leucocytes: their absence later was almost certainly due to destruction and not to any failure of the leucocytic response. This is borne out by sections of the uterus from such cases, which, in the decidua at least, always showed abundant leucocytes.

The smears represented in Figures 2, 3, and 4 were from patients with well established severe infections.

In every case in which the symptoms typical of a severe Clostridium welchii infection developed after the patient's admission to hospital and in which investigations were carried out prior to such development, the cervical smears suggested a severe infection before it

was possible to arrive at a clinical diagnosis.

In more than 150 control cases, i.e. those in which infection with the Clostridium welchii was localized to the contents of the uterus or those with Clostridia welchii in the blood stream but without the symptoms characteristic of a severe infection due to this organism, there was not a single instance in which the smears showed heavily capsulated Clostridia welchii as well as damage to the leucocytes. Fourteen patients in this group had smears in which there were many capsulated Clostridia welchii, but in each instance recovery took place without specific treatment for Clostridia welchii even though 4 patients showed one or other of the symptoms usually associated with the severe infections.

When there were only a few capsulated Clostridia welchii in the cervical smear, their significance was sometimes in doubt, since in the early stage of the severe infections the leucocytes usually appeared undamaged when only a small number of the Clostridium welchii was present. Reference to the apparent size and structure of the capsules was helpful in assessing such smears. In the severe infections the smears always showed forms with the capsule around the bacillus at least as wide as the rod itself, and frequently very heavily capsulated bacilli with the width of the capsule greater than the rod.

In smears from the cases with blood destruction, the dimensions of the majority of the capsulated rods were 2 to 3μ in length, 1 to 1.2μ in width, and the fragile capsular material at the sides of the rod varied from 1 to 1.5μ. In 3 cases, however, the Clostridia welchii were larger, many of the bacilli being 4μ in length and a few longer. In smears from the severe infections characterized by collapse the dimensions were different. Approximately half of the bacilli were found to measure 4μ in length with a width varying from 0.5 to 0.8 μ and the width of the capsules ranged from 0.8 to 1.8μ.

In addition to these types of well capsulated Clostridia welchii there were forms similar to those already described as occurring in broth cultures (Fig. 1), in which the capsule completely obscured the rod. These obscured forms varied in length from 1.5 to 4μ and in width from 1 to 2.5μ. Originally all the obscured forms were regarded as heavily capsulated and therefore suggestive of the presence of a strain sufficiently invasive to cause a severe infection. But it is now apparent that only those obscured forms not less than 2μ in width and in which the difference between length and breadth is not great cause severe infections. The comparatively long and narrow obscured forms (usually 2 to 4μ by 1 to 1.5μ) are not highly invasive.

Even when these points of differentiation are borne in mind, repetition of the smear is often necessary to determine the significance of a few capsulated Clostridia welchii in the cervical smear. The number of Clostridia welchii to be seen in the smears and the damage to the leucocytes will increase rapidly if the strain is sufficiently invasive to cause a severe infection. In some cases a dramatic change occurs in a few hours: in others a period of 12 hours, rarely longer, may elapse before a smear typical of a severe infection is obtained.

The significance of uncapsulated Clostridium welchii. The presence of uncapsulated Clostridia welchii in the cervical smear even in large numbers is of no serious import. Not one instance of a severe Clostridium welchii infection was recorded among more than 100 cases with Clostridia welchii in the genital tract, in which only uncapsulated rods were present in the cervical smears.

The effect of other bacteria. The presence of other bacteria does not interfere with the recognition of the degree of capsulation of Clostridium welchii strains. Figure 2 shows typical capsulated Clostridia welchii in the presence of many cocci.

Very few of the bacteria other than Clostridia welchii which are associated with abortional infections cause appreciable damage to the leucocytes. Of the aerobic bacteria, only the highly virulent strains of the Streptococcus haemolyticus Group A cause significant cell destruction, and this not often. The presence of such streptococci should not be a serious source of error since the majority of the highly virulent strains of Streptococcus haemolyticus Group A can be recognized by their heavy

capsules when a smear is stained with Leishman's stain (5).

Of the anaerobic bacteria other than Clostridia welchii only the Clostridia septique was observed to cause damage to the leucocytes, and only some strains possess this property. In 4 out of 6 cases harboring both these clostridia, a severe infection with Clostridia welchii could be excluded because of lack of damage to the leucocytes, although in one instance the Clostridia welchii were heavily capsulated. In the other 2 cases the smears showed considerable damage to the leucocytes but in one the Clostridia welchii, although heavily capsulated, were more readily phagocytosed than is usual in the severe Clostridium welchii infections; for this reason the case was regarded as primarily an infection with Clostridia septique. The smears from the remaining case showed in addition to the leucocytic damage the capsulation and resistance to phagocytosis typical of the severe Clostridium welchii infections. In this instance the Clostridia welchii were considered to be of greater importance than the Clostridia septique.

The reliability of cervical smears for the diagnosis of the severe abortional infections due to Clostridia welchii can be gauged by the fact that in this hospital during the last 3 years no patient has been treated for a Clostridium welchii infection unless the cervical smear suggested that the infecting strain was highly invasive, and during this period no patient who failed to show typical smears died from a Clostridium welchii infection.

Correlation of symptoms with certain characteristics of the cervical smear. Not only is there this close correlation between the severity of infection and the appearance of the cervical smear, but there are further points of difference in the smears corresponding to the patient's outstanding symptoms. In cases in which gross blood destruction occurred, the majority of the Clostridia welchii in the smears were short, stout rods lying singly or in pairs, and the capsules were fragile (Fig. 3).

In cases in which collapse and not blood destruction was outstanding the Clostridia welchii were quite different in appearance; they were longer, thinner, and the capsules had a clearly defined outline (Fig. 4).

Further evidence of the association between collapse and the thin type of Clostridia welchii was afforded by the observation that in a few of the abortional cases with a mild localized Clostridium welchii infection, signs of shock developed for which there appeared no cause other than that of the infection. In these instances the Clostridia welchii in the cervical smears were long and thin.

These various correlations offer strong support for the view that the nature of the infecting strain is of prime importance in determining the severity and type of infection. The results of cultural studies to be discussed later also support this opinion.

Posttraumatic and postoperative infections. Although direct smears have been examined from only 16 wounds harboring Clostridia welchii, it is already clear that heavy capsulation, rapid increase in the number of Clostridia welchii in serial smears, and damage to the leucocytes point to an actively invasive infection. Conversely, poor capsulation, failure of Clostridia welchii to increase rapidly, active phagocytosis, and lack of leucocytic damage all indicate that a severe invasive infection is unlikely; when two or more of these factors are observed they constitute very strong evidence against the diagnosis of Clostridium welchii gas gangrene.

In smears from this series of wound infections, the criterion of heavy capsulation was the same as that already described for the abortional cases. As with the latter infections, obscured forms that were long and narrow were not considered to be sufficiently well capsulated to indicate the presence of an invasive strain.

In 3 cases of rapidly fatal gas gangrene, 2 following minor injuries, the smears resembled those of the severe abortional infections. In the other 3 cases of gas gangrene from which smears were examined, the amount of leucocytic damage was less than in the fulminating wound infections and in the severe abortional types.

In 3 cases of localized Clostridium welchii infection unaccompanied by severe toxemia the smears showed a few heavily capsulated bacilli in 2, and a moderate number of the long, thin type in the third, but the leucocytes

TABLE I.—SUMMARY OF FINDINGS IN 16 CASES

Characteristics of the smears			6 cases of gas gangrene due to Cl. welchii	3 cases of localized Cl. welchii infection without severe toxemia	7 cases of wounds "contaminated" with Cl. welchii
No. of Cl. welchii	Capsulation	Damage to leucocytes			
Many	Heavy	+	6		
Many	Long obscured type	—		1	1
Few	Heavy	—		2	
Few	Long obscured type	—			2
None		—			4

were not appreciably damaged. In 3 cases in which the Clostridium welchii appeared to be mere contaminants in the wound and were probably only multiplying in dead tissue, the capsulated bacilli present were of the long obscured type and were unaccompanied by evidence of leucocytic damage. There were 4 other cases without clinical signs of Clostridium welchii infection in which Gram positive bacilli resembling this bacterium were not seen in the direct smears although the Clostridium welchii was cultivated from the same material. The findings in these 16 cases are summarized in Table I.

The presence of heavily capsulated Clostridia welchii in a smear taken from those areas of a wound where spread of infection is suspected should probably always be regarded as suggestive of gas gangrene, but repetition of the smears may be necessary to determine the leucocytic damage and should always be undertaken when only a small number of Clostridia welchii are present.

If the repeated smears show only a few Clostridia welchii this is an indication that up to that time a severe infection due to this organism has not developed. Increasing damage to the leucocytes in the absence of an increased number of typical Clostridia welchii should be regarded only as indicative of a severe infection with this organism if the smears fail to reveal the presence of other highly pathogenic bacteria. Caution is needed in interpreting an increased number of Clostridia welchii in the absence of recognizable damage to the leucocytes. Such a finding might be compatible with the early stages of gas gangrene but is certainly not typical of a well established severe infection.

MacLennan, in his article on anaerobic infections of war wounds, laid particular stress on the need for differentiation between gas gangrene (clostridial myositis) and the type of clostridial infection which is unaccompanied by severe toxemia (anaerobic cellulitis). The experience of this laboratory suggests that these two conditions, when due to Clostridium welchii infection, could probably be distinguished by reference to the type and extent of capsulation and the state of the leucocytes as revealed in stained smears.

I have not seen an instance of uncapsulated Clostridia welchii in the smear from a wound, but it appears probable that such strains are unimportant.

THE BEHAVIOR OF THE CLOSTRIDIUM WELCHII IN CULTURE AS A GUIDE TO THEIR SIGNIFICANCE

Infections following abortion. Work carried out in this laboratory has shown that cultures of the variants of Clostridia welchii responsible for the severe infections possess certain characteristics which help to differentiate them from the strains which are relatively harmless (1, 3). The strains associated with the severe infections have invariably been very heavily capsulated when grown in Wright's broth containing minced veal, while nearly 90 per cent of the strains isolated from cases without symptoms of a severe Clostridium welchii infection have shown much less capsular material. Indeed, more than half of the latter strains have failed to produce any but the smallest amounts of stainable capsular material when grown in the absence of serum. These statements are based on an examination of more than 800 strains.

These results confirm the conclusion drawn from the examination of direct smears that only heavily capsulated strains cause serious infections.

Keppie and Robertson (1944) working with 3½ hour cultures of Clostridium welchii strains grown in a broth containing both serum and glucose, and using the India ink method (negative staining) to demonstrate capsulation, concluded that a narrow capsule indicated

good toxigenic ability; a wide capsule in most cases poor toxigenicity. Using this technique they found that strains present in wounds as harmless contaminants showed the widest clear zones around the bacilli.

This finding must not be interpreted as being opposed to the view expressed in this paper that the heavier the capsulation the more likely is the strain to be highly pathogenic. In all work in this laboratory capsulation has been demonstrated by staining the capsules by the method of Richard Muir and not by the negative staining of the India ink method. When these two methods are applied to the same series of cultures the apparent width of capsule around the bacterial rod is not always the same.

In a recent experiment in which smears from young cultures of 50 strains of Clostridium welchii were examined by both methods, the results were discrepant with 15 of the strains, 7 showed medium or wide zones with India ink but only narrow capsules with Muir's stain, and in 8 smears the reverse was observed.

Growth characteristics, resistance to phagocytosis, and, to a small extent, α toxin production in culture also serve as indications of the significance of a strain of Clostridium welchii. The most useful growth characteristics were obtained by using Huntoon's hormone agar plates (containing rabbit's blood) and serum-neopeptone-water (50% horse serum). Details of the methods and of the results have been published (1, 3).

All but 3 of 40 strains causing the severe infections with blood destruction gave smooth surface colonies, nongranular growth in the serum-neopeptone-water, were resistant to phagocytosis in defibrinated human blood, and were active producers of α toxin (the other toxins of Clostridia welchii were not studied). Five strains associated with infections characterized by collapse were unstable in regard to colony form; the predominant type was smooth or intermediate smooth but flattened colonies with ringed edges were also present. These strains produced a granular deposit in serum-neopeptone-water, were re-resistant to phagocytosis and produced comparatively little α toxin.

The correlation between severity of infection and any one of the above characteristics was not absolute. Of 285 strains which had not given rise to a severe infection 57 (20%) gave smooth surface colonies and a nongranular type of growth in serum-neopeptone-water, thus resembling the strains causing the majority of the severe infections. Similarly, 30 per cent of strains not associated with severe infections were resistant to phagocytosis. But only 5 per cent of the strains which had not caused severe infections were very heavily capsulated in broth, produced smooth surface colonies and were resistant to phagocytosis.

Certain individual findings, however, do brand a strain as harmless. A strain which when first isolated produces no capsular material in Wright's broth has not yet been found responsible for a serious uterine infection. Similarly, a strain that produces only completely rough flat colonies, or one which is very readily phagocytosed when freshly isolated can be ruled out as a cause of uterine infection that is capable of producing clinical signs.

Posttraumatic and postoperative infections. Tests similar to those used for the cultures from the abortional cases were applied to the Clostridia welchii isolated from 26 cases of infected wounds.

In 8 instances the patient suffered from gas gangrene due primarily to infection with this organism. In 7, the Clostridium welchii was the only clostridium isolated; in the remaining one the Clostridium bifermentans was also present. Considered as a group, the Clostridia welchii strains from these 8 cases differed in colony form from the strains causing the severe abortional infections characterized by blood destruction, and in α toxin production from the strains causing the rapidly fatal "collapse" cases.

In smears from cultures, the bacilli were stout, square-ended, and heavily capsulated. On the Huntoon's plates only 1 strain gave perfectly smooth surface colonies; 6 were unstable, producing either smooth or intermediate smooth colonies a proportion of which showed flat rough outgrowths; the remaining strain produced intermediate smooth colonies only. A nongranular type of growth was pro-

TABLE II.—SUMMARY OF FINDINGS IN 26 STRAINS

Characteristics of cultures			8 cases of gas gangrene due to Cl. welchii	3 cases of localized Cl. welchii infection without severe toxemia	7 cases of wounds "contaminated" with Cl. welchii	8 cases of infected wounds yielding Cl. welchii + other clostridia
Capsulation in broth	Surface colony form	Resistance to phagocytosis in human defibrinated blood				
Heavy	S. or I.S.	+	2			2
Heavy	Unstable S. or I.S.	+	6		3	1
Heavy	Unstable S. or I.S.	—		1		
Heavy	I.R.	+		1		
Heavy	I.R.	—				1
Slight	I.S.	—			1	3
Slight	I.R.	—			3	1

S. = Smooth. I.S. = Intermediate smooth.
I.R. = Intermediate rough. See Butler (1).

duced in serum-neopeptone-water, sometimes with a flaky deposit. These strains were resistant to phagocytosis and were with 1 exception active producers of α toxin.

Two out of 3 strains isolated from cases of localized Clostridium welchii infection unaccompanied by severe toxemia differed from the strains associated with gas gangrene, one by producing intermediate rough surface colonies and a granular type of growth in serum-neopeptone-water and the other in its susceptibility to phagocytosis.

Of 7 strains which appeared to be mere contaminants of wounds, 3 could not be distinguished in culture from those of the gas gangrene cases, but in each instance direct smears showed that neither the capsulation nor the leucocytic damage was typical of a severe infection. The other 4 strains were only slightly capsulated in broth and readily phagocytosed; 3 of these strains produced intermediate rough and 1 intermediate smooth surface colonies.

The remaining 8 strains of Clostridia welchii in this series were from infected wounds which also showed other clostridia, the details of which were not available to me. Three strains resembled those associated with the known cases of gas gangrene due to Clostridia welchii, but the other 5 were readily phagocytosed, and 4 were poorly capsulated. This suggested that in 5 cases, 2 of which were fatal gas gangrene, it was anaerobes other than Clostridia welchii which were the important infecting agents.

The findings in regard to capsulation in broth culture, surface colony form, and resistance to phagocytosis of the 26 strains isolated from wounds are summarized in Table II, reference to which suggests that these characteristics are a less reliable indication of the significance of the Clostridium welchii in a wound than the appearance of the direct smear.

In 1 case in this series gas gangrene was accompanied by jaundice and hemoglobinuria. This was the only instance among the traumatic infections in which both the direct smears and the cultural characteristics of the infecting strain were indistinguishable from those of the severe abortional infections with blood destruction. A further parallel was the recovery of the Clostridium welchii from the blood and urine during life.

THE MODE OF DEVELOPMENT OF CLOSTRIDIUM WELCHII INFECTIONS

The studies of abortional infections showed that the invasiveness of the infecting strain was of paramount importance in the development of the severe Clostridium welchii infections. This finding, coupled with the observation that many freshly isolated strains of the Clostridium welchii were pathogenic for guinea pigs when a toxin-free inoculum was used, focused attention on the mode of development of infection in man (4).

In the past our understanding of Clostridium welchii infection has been retarded by too much stress being placed on the significance of the exotoxins. It was assumed that the bacilli themselves were not invasive and that therefore their introduction into wounds caused serious infection only in the presence of considerable tissue damage, of foreign bodies, of interference with the blood supply, etc.

The occurrence of gas gangrene due to Clostridia welchii, often of a fulminating type, following the hypodermic injection of a bland substance or after any other trivial injury is evidence that with some strains the mere in-

troduction of the organisms into the tissues will initiate a serious infection.

The recent papers of Robertson and Keppie (1941 and 1944) show that toxin production alone, as measured by *in vitro* tests, does not satisfactorily explain the behavior of Clostridia welchii when present in wounds, and in our experience toxin production alone has not provided a satisfactory indication of the severity of the abortional infections.

Two other observations support the hypothesis that the Clostridium welchii in its attack on human tissues is not dependent only on its power to produce lethal exotoxins. First, the study of abortional infections in general reveals certain points of similarity between the fulminating infections with Streptococcus haemolyticus Group A and those due to the Clostridium welchii. In both, the infection becomes rapidly generalized and positive blood cultures are usually obtained in the early stages of the illness. In both, there is a correlation between severity of infection and intense capsulation of the infecting strain.

Second, the exotoxins of Clostridia welchii are weak in comparison with those of some of the other highly pathogenic clostridia and yet gas gangrene due to Clostridia welchii usually develops more rapidly than do the infections caused by the other anaerobes. This latter observation is in keeping with the view that the Clostridium welchii is a potentially invasive organism because of its possession of a capsule.

In a previous publication I have suggested that a better understanding of Clostridium welchii infections is afforded if we regard the strains of this organism as divisible into groups according to the invasiveness of the bacilli themselves. A study of some hundreds of freshly isolated strains of Clostridia welchii and a consideration of the lesions which are produced in the patients by these organisms, has led me to suggest the following 3 groups (4).

The first and most important group consists of those strains which are so highly invasive that they can attack undamaged tissue. Judging by the experience of this laboratory the majority of such strains produce smooth surface colonies, are extremely heavily capsulated, and are completely resistant to phagocytosis. These highly invasive variants are comparatively rare.

Second, there are strains of moderate invasive power; they do not readily invade undamaged tissue, but apparently can spread rapidly in damaged areas, where they produce sufficient exotoxin to damage adjacent tissue and thus cause a spreading infection. In the absence of extensive tissue damage, strains such as these are unlikely to cause serious infection in man. These strains show some, but not all, of the characteristics of highly invasive variants. They are heavily capsulated, although as a group less so than the highly invasive variants, and are either completely or moderately resistant to phagocytosis by human leucocytes. As a rule they do not produce typically smooth colonies on Huntoon's hormone agar plates after 48 hours' incubation.

Third, there are strains of low invasive power which apparently multiply only in dead tissue and cannot invade adjacent areas even if these are damaged by toxin, so that a spreading infection is never produced by such strains. Usually these strains produce rough colonies, are poorly capsulated, and readily phagocytosed. Occasionally a strain of low invasiveness possesses one, but never several, of the characteristics of more virulent organisms.

Work on the invasiveness of the Clostridium welchii strains is still in progress and further experience may well modify some of our present opinions, but not, I think, our view of the importance of the invasiveness of the Clostridium welchii bacilli and of the practical significance of the degree of capsulation and damage to the leucocytes as revealed in smears from the possibly infected area.

The importance of the invasiveness of the Clostridium welchii apart from the exotoxins produced has received scant, if any, attention from recent writers. MacLennan (1943) in his articles on anaerobic infections of war wounds did not stress this point, with the result that some of his views are almost certainly not applicable to infections caused by the Clostridium welchii alone.

For example this author's statement that the clostridia are primarily and essentially

saprophytes is too sweeping as long as the Clostridium welchii is included in the group. Apart from the experimental evidence I find it impossible to regard the Clostridium welchii as essentially a saprophyte in view of, first, the occurrence of rapidly fatal infections following hypodermic injections, and, second, the occurrence in the presence of severe abortional infections of invasion of the blood stream in the early stage of the disease, usually in the absence of extensive damage to the uterus.

The view that the development of Clostridium welchii infection in man is largely dependent on the invasiveness of the bacilli themselves, has an important bearing on other points raised by MacLennan. This author pointed out that neither in prevention nor in treatment had much advance been made in the last 25 years in spite of the increase in the potency of antisera. While this statement was made in regard to gas gangrene generally, available evidence shows that it is particularly true for Clostridium welchii infections. This fact is another argument against the hypothesis that the toxigenicity of the infecting organism is all important. Once it is realized that, in the severe types of Clostridium welchii infection, the invasive power of the bacilli themselves is of considerable importance, it is apparent why improvements in antisera have not produced startling results. In earlier work carried out in this laboratory it has been shown experimentally that invasiveness is only partially influenced by antitoxin.

Again, MacLennan stated that on "theoretical grounds gas gangrene should be eminently preventable by surgical methods alone; yet such has certainly not been the case." Clearly here is another good reason for discarding the old idea that Clostridia welchii bacilli themselves are nonvirulent and therefore cannot invade any but grossly damaged tissue.

APPLICATION TO THERAPY AND RESEARCH

The earlier sections of this paper have described the use of direct smears, and to a lesser extent the use of cultures, for the rapid detection of Clostridia welchii and as a means of determining the significance of this organism.

These tests can therefore be used as a guide for treatment. In a case with clinical signs of gas gangrene or other type of clostridial infection, smears typical of a severe infection with Clostridia welchii will indicate the need for instituting full treatment against this organism, whereas if the smear does not suggest a severe infection it focuses attention on the possibility of some other agent causing the patient's symptoms. Thus a more extensive examination of the smears may show clostridial forms resembling Clostridium septique or an infection with anaerobic streptococci or the Streptococcus haemolyticus Group A.

Direct smears should play a large part in the management of the case in which the Clostridium welchii is detected in a wound but which at that time does not show clinical signs of gas gangrene. In such cases it would be logical to withhold specific treatment as long as the smears did not suggest an actively invasive infection.

Only limited use has so far been made of direct smears. MacLennan (1943) stressed the usefulness of a Gram stained smear in the diagnosis of gas gangrene. But if the Clostridium welchii is the infecting organism this is not enough; in such cases it is essential to use a stain which shows the capsules and does not distort or fail to stain the leucocytes. In the Medical Research Council's War Memorandum on gas gangrene (1943), the significance of the findings in Gram stained smears from wounds was discussed in some detail, but no mention was made of the demonstration of Clostridium welchii capsules to determine either the presence or the significance of this clostridium. Reed and Orr (1943), in their article on the progress of medical science in relation to gas gangrene, mentioned the making of Gram stained smears at the same time as attempts at cultivation were undertaken, but did not suggest the use of direct smears for the rapid diagnosis of Clostridium welchii infections.

Failure to recognize the importance of bacteriological methods for the diagnosis of severe Clostridium welchii infections is apparent in two recent articles on puerperal infections.

In that of Rendle-Short (1942) the criteria for the bacteriological diagnosis of the severe Clostridium welchii infections were not discussed, and in Salm's paper, "The Occurrence and Significance of Clostridium Welchii in the Female Genital Tract" (1944), no mention was made of any laboratory method for assessing the significance of the presence of this organism.

To determine the value of any particular form of treatment in serious Clostridium welchii infections, knowledge of the invasiveness of individual strains is essential. Any claim of success is quite without justification if cases are included in which the Clostridium welchii detected lacked the necessary invasiveness.

Knowledge of the invasiveness of individual strains is also important for the evaluation of prophylactic measures. Without such an assessment exaggerated claims may be made since any method will succeed if only harmless strains are present.

Since in the severe Clostridium welchii infections the invasiveness of the bacilli themselves is as important as toxin production, treatment should be directed against both aspects. There can be little doubt that antitoxin must be employed in all Clostridium welchii infections that warrant treatment, but in cases in which the smears indicate the presence of a highly invasive strain, therapy with an antibacterial agent effective against such variants is also necessary.

In planning experimental work designed to test therapeutic substances, full consideration should be given to all the properties of the strain used as the infecting agent. In a previous article (4) I have pointed out that many of the reports dealing with the treatment of experimental Clostridium welchii infections with the sulfonamides prove but little since the strains used were not fully described and the time elapsing since their isolation was not given.

This latter point is most important. Work in this laboratory has shown that many freshly isolated strains of Clostridia welchii from human sources are pathogenic for guinea pigs when washed cultures are used. But this property is fairly rapidly lost, with some strains in less than 3 months. Similarly, resistance to phagocytosis by human leucocytes may quickly disappear during artificial cultivation.

Further evidence of the necessity for using freshly isolated strains has been provided by recent experiments in rats carried out in this laboratory. When rats were infected with a freshly isolated strain from a fatal abortional infection, the administration of antitoxin alone failed to save more than a small proportion of the animals, while treatment with both antitoxin and an antibacterial agent was highly successful. Repetitions of these experiments over several months showed a decrease in the virulence of the strain as evidenced by an increasingly larger proportion of survivors in the group treated with antitoxin alone.

SUMMARY

1. The rapid identification of the Clostridium welchii by the demonstration of stained capsules is described. The method has been successfully applied to smears from broth cultures as well as from tissues suspected of harboring this clostridium.

2. Methods for determining the significance of the presence of Clostridia welchii in relation to abortional and posttraumatic infections are discussed. In both types of infection it was found that the degree of capsulation together with the extent of the damage to leucocytes as revealed in direct smears provided a reliable indication of the severity of infection. It is concluded that the examination of smears from the suspected infected area is the most rapid and most reliable means for the bacteriological diagnosis of the severe types of Clostridium welchii infection.

3. The development of Clostridium welchii infection in man is discussed, and it is suggested that the invasiveness of the bacilli themselves, apart from toxin production, largely conditions the occurrence of clinically recognizable infection.

4. The application of these methods and conclusions to therapy and research is indicated.

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AN EXPERIMENTAL EVALUATION OF AMERICAN COMMERCIAL BIVALENT AND PENTAVALENT GAS GANGRENE ANTITOXINS

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A REVIEW of the history of malignant edema and gaseous gangrene (2) shows that most surgeons who have had experience in the use of gas gangrene antitoxins favor their use but there have been a few who have not been so impressed. One suspects that in some instances those who have condemned the use of serum have failed to distinguish between its prophylactic and therapeutic values, that perhaps in some cases the serum has not been used until symptoms were far advanced, and then in quantities too small to be of value, or under other unfavorable conditions.

This writer believes that gas gangrene serum is not needed at all for wounds which receive prompt adequate surgery, that its principal value is prophylactic to prevent or delay anaerobic infection until adequate surgery can be secured, that it can never take the place of adequate surgery, and that for these reasons it is much more important in relation to war wounds than in relation to civilian wounds. But he believes also that it has definite therapeutic values when used in adequate dosage as an adjunct to surgery in the treatment of malignant edema and gaseous gangrene due to anaerobic bacilli.

Early in our study of civilian wounds, the writer was asked to make a study of commercial gas gangrene antitoxins. Specimens of these were furnished by seven manufacturers. They came in small rubber capped bottles or syringes each containing one therapeutic dose. The different brands will be designated by the letters A, B, C, D, E, F, and G.

From the Central Laboratory of the Contaminated Wound Project, College of Physicians and Surgeons, Columbia University.

This work was done under a contract recommended by the Committee on Medical Research, between the Office of Research and Development and Columbia University, New York, New York.

Dr. Frank L. Meleney of the Subcommittee on Surgical Infections was the Responsible Investigator.

The contents of these containers were in all cases clear or only slightly opalescent liquids and remained so on storage in an electric refrigerator for more than 2 years without any visible evidence of deterioration. All of the tests were made before the dates of expiration printed on the labels.

Serum B, the only pentavalent antitoxin, had the following stated potency:

Bacillus perfringens antitoxin	10,000 units
Bacillus septicus antitoxin	10,000 units
Bacillus histolyticus antitoxin	3,000 units
Bacillus novyi antitoxin	1,500 units
Bacillus sordellii antitoxin	1,500 units

It is to be understood that these are international units but, as I have recently shown (3), no two of these standard international units are defined alike in terms of minimal lethal doses of toxin neutralized. Granting that it is possible to define antitoxin units in terms of minimal lethal doses only approximately, we find that the approximate protective power in terms of mouse minimum lethal dose of toxins which are represented in this "therapeutic dose" of antitoxin is as tabulated in the following:

Bacillus perfringens toxin	500,000 to 700,000
Bacillus septicus toxin	400,000 to 640,000
Bacillus histolyticus toxin	about 135,000
Bacillus novyi toxin	about 7,500,000
Bacillus sordellii toxin	2,850,000 to 5,700,000

All of the other serums were bivalent, each therapeutit dose containing 10,000 units of Bacillus perfringens antitoxin and 10,000 units of Bacillus septicus antitoxin.

EXPERIMENTS ON BACILLUS PERFRINGENS

Since Bacillus perfringens is the commonest single cause of gaseous gangrene, experiments were started in the first place with toxin, and subsequently living cultures of this microorganism were used.

TABLE I.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST TOXIN OF BACILLUS PERFRINGENS

Dose of toxin 1 c.c.; dose of antitoxin 1 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum in c.c.	Lesions	Final result
66	370	1	—	—	Edema, lysis, rupture, eschar	Recovery
68	330	0.5	—	—	Edema, lysis, no rupture, eschar	Recovery
67	320	0.25	—	—	Marked edema, lysis, rupture, eschar	Recovery
70	315	0.125	—	—	Moderate edema, lysis, adherent scab, secondary infection	Dead in 11 days
71	315	1	A	1	None	Lived
64	315	1	B	1	None	Lived
63	310	1	C	1	None	Lived
69	310	1	D	1	Slight transient edema	Lived
62	310	1	E	1	None	Lived
65	300	1	F	1	None	Lived
56	215	1	G	1	None	Lived

TABLE II.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST TOXIN OF BACILLUS PERFRINGENS

Dose of toxin 1 c.c.; dose of antitoxin 0.1 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum in c.c.	Lesions	Final result
95	455	1	—	—	Edema, lysis	Dead in 22 hrs.
85	355	0.5	—	—	Marked edema, lysis, rupture of skin, eschar, abdominal perforation	Dead in 14 days
87	355	0.25	—	—	Marked edema, no lysis, eschar	Recovered
89	345	0.125	—	—	Marked edema, no lysis, at 3 days, eschar, abdominal perforation	Dead in 10 days
92	335	1	A	0.1	None	Lived
90	340	1	B	0.1	None	Lived
86	330	1	C	0.1	None	Lived
93	330	1	D	0.1	None	Lived
88	320	1	E	0.1	None	Lived
94	320	1	F	0.1	None	Lived
91	305	1	G	0.1	None	Lived

EXPERIMENTS WITH THE TOXIN OF BACILLUS PERFRINGENS

A toxin prepared by Dr. M. A. Logan of the University of Cincinnati was supplied. It was packed in ice and shipped by airplane July 18, 1942. This toxin was stated to contain about 1,000 units of alpha-toxin per cubic centimeter as determined by Van Heyningen's method *in vitro*. It was said to have been preserved with phenylmercuric acetate and appeared as a clear light golden liquid with a light sediment of crystals resembling those of tyrosine. It was sterile. We always stored it in an electric refrigerator kept at 2 degrees C.

July 22, 1942, a guinea pig weighing 605 grams was injected with 1 cubic centimeter of this toxin subcutaneously. This animal developed marked subcutaneous edema with liquefying necrosis overnight. On the following day the edema was apparently subsiding but the animal was very sick and died about noon. Its belly wall was full of maggots but there was no evidence of penetration of the abdomen. The abdominal viscera appeared to be normal but the lungs were congested.

A smaller guinea pig, weighing 245 grams, was injected subcutaneously with 1 cubic centimeter of the same toxin, boiled 2 minutes. This animal developed overnight marked subcutaneous edema without liquefaction but recovered.

A guinea pig weighing 225 grams inoculated with 0.1 cubic centimeter of unboiled toxin subcutaneously, developed marked edema overnight which became severe at 48 hours. At 72 hours there was liquefying necrosis and at 96 hours the skin ruptured, after which an eschar formed. This scar sloughed in 16 days leaving a clean healthy granulating area which eventually healed.

A guinea pig weighing 285 grams given 0.01 cubic centimeter of toxin had a moderate edema and followed a course to recovery similar to that of the preceding animal.

Experiment 1. October 1, 1942, a series of guinea pigs was injected with freshly made mixtures of 1 cubic centimeter of this toxin and 1 cubic centimeter of the various serums. Four control animals, all but one heavier than those receiving mixture, received graded doses of toxin alone. Table I summarizes data.

TABLE III.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST TOXIN OF BACILLUS PERFRINGENS

Dose of Toxin 1 c.c. Dose of antitoxin 0.01 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum in c.c.	Lesions	Final result
112	385	1	—	—	Edema, lysis, no rupture of skin	Dead in 40 hours
116	380	0.2	—	—	Marked edema, lysis 4th day, no rupture of skin, eschar	Recovered
117	375	0.1	—	—	Marked edema 2d day, lysis, eschar	Recovered
122	365	0.05	—	—	Marked edema 2d day, lysis, eschar	Recovered
114	365	1	A	0.01	None	Lived
123	365	1	B	0.01	None	Lived
113	355	1	C	0.01	Marked edema, lysis, no rupture of skin, prostrate 4th day	Dead in 5 days
120	345	1	D	0.01	None	Lived
124	345	1	E	0.01	None	Lived
118	330	1	F	0.01	Marked edema, lysis, no rupture of skin, eschar	Recovered
121	315	1	G	0.01	None	Lived

TABLE IV.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST TOXIN OF BACILLUS PERFRINGENS

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum in c.c.	Lesions	Final result
134	305	1	—	—	Marked edema, lysis	Dead in 5 days
132	305	0.2	—	—	Marked edema, lysis, adherent scab	Dead in 18 days
133	275	0.1	—	—	Marked edema, eschar	Recovered
137	245	0.05	—	—	Marked edema, lysis, rupture of skin, eschar	Recovered
135	255	1	A	0.001	Moderate edema, lysis	Dead in 24 hours
119	255	1	B	0.001	Edema, lysis, eschar	Recovered
131	240	1	C	0.01	Edema	Dead in 3 days*
128	220	1	D	0.001	Moderate edema	Dead in 24 hours
126	245	1	E	0.001	Edema, no lysis	Dead in 48 hours
125	240	1	F	0.01	None	Lived‡
129	215	1	G	0.001	Edema, lysis, eschar	Recovered

*Confirming result in Experiment 3.
‡Not confirming result in Experiment 3.

Table I shows that all of the controls developed the characteristic edema with subcutaneous lysis, rupture of the skin in 2 cases, recovery in 3 and death after 11 days by secondary infection of an adherent scab in the case of the animal that received the smallest dose of toxin.

One of the test animals developed a slight transient edema; none of the rest showed any symptoms.

Experiment 2. October 23, 1942, a series of guinea pigs was injected with mixtures of 1 cubic centimeter of toxin and 0.1 cubic centimeter of each of the antitoxins, along with 4 of the heaviest animals as controls, receiving graded doses of toxin. The data are summarized in Table II.

Table II shows that the test dose of 1 cubic centimeter killed a large guinea pig in less than 22 hours while marked lesions were produced with smaller doses down to 0.125 cubic centimeter and 2 of these animals also died later with abdominal perforations.

None of the test animals receiving 0.1 cubic centimeter of the various serums showed any effects whatever.

Experiment 3. November 4, 1942, a series of guinea pigs was injected with mixtures of 1 cubic centimeter of toxin and 0.01 cubic centimeter of each of the antitoxins, along with the usual controls. The data are summarized in Table III.

Table III shows that the test dose of 1 cubic centimeter killed a large normal guinea pig in about 40 hours. Guinea pigs receiving smaller doses down to 0.05 cubic centimeter all showed characteristic lesions but recovered.

Five of those receiving mixtures of 1 cubic centimeter of toxin and 0.01 cubic centimeter of antitoxin showed no result, but in 2 instances this dose of antitoxin failed to protect against the development of the usual lesions; 1 of these guinea pigs died on the 5th day but the other one recovered slowly.

Experiment 4. November 19, 1942, a series of guinea pigs was injected with mixtures of 1 cubic centimeter and 0.001 cubic centimeter of antitoxin, except that in the case of antitoxins C and F, 0.01 cubic centimeter was used to recheck the results in Experiment 3. The usual controls were used. The results are shown in Table IV.

TABLE I.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST TOXIN OF BACILLUS PERFRINGENS

Dose of toxin 1 c.c.; dose of antitoxin 1 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum in c.c.	Lesions	Final result
66	370	1	—	—	Edema, lysis, rupture, eschar	Recovery
68	330	0.5	—	—	Edema, lysis, no rupture, eschar	Recovery
67	320	0.25	—	—	Marked edema, lysis, rupture, eschar	Recovery
70	315	0.125	—	—	Moderate edema, lysis, adherent scab, secondary infection	Dead in 11 days
71	315	1	A	1	None	Lived
64	315	1	B	1	None	Lived
63	310	1	C	1	None	Lived
69	310	1	D	1	Slight transient edema	Lived
62	310	1	E	1	None	Lived
65	300	1	F	1	None	Lived
56	215	1	G	1	None	Lived

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87	355	0.25	—	—	Marked edema, no lysis, eschar	Recovered
89	345	0.125	—	—	Marked edema, no lysis, at 3 days, eschar, abdominal perforation	Dead in 10 days
92	335	1	A	0.1	None	Lived
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A guinea pig weighing 225 grams inoculated with 0.1 cubic centimeter of unboiled toxin subcutaneously, developed marked edema overnight which became severe at 48 hours. At 72 hours there was liquefying necrosis and at 96 hours the skin ruptured, after which an eschar formed. This scar sloughed in 16 days leaving a clean healthy granulating area which eventually healed.

A guinea pig weighing 285 grams given 0.01 cubic centimeter of toxin had a moderate edema and followed a course to recovery similar to that of the preceding animal.

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120	345	1	D	0.01	None	Lived
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Table I shows that all of the controls developed the characteristic edema with subcutaneous lysis, rupture of the skin in 2 cases, recovery in 3 and death after 11 days by secondary infection of an adherent scab in the case of the animal that received the smallest dose of toxin.

One of the test animals developed a slight transient edema; none of the rest showed any symptoms.

Experiment 2. October 23, 1942, a series of guinea pigs was injected with mixtures of 1 cubic centimeter of toxin and 0.1 cubic centimeter of each of the antitoxins, along with 4 of the heaviest animals as controls, receiving graded doses of toxin. The data are summarized in Table II.

Table II shows that the test dose of 1 cubic centimeter killed a large guinea pig in less than 22 hours while marked lesions were produced with smaller doses down to 0.125 cubic centimeter and 2 of these animals also died later with abdominal perforations.

None of the test animals receiving 0.1 cubic centimeter of the various serums showed any effects whatever.

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133	275	0.1	—	—	Marked edema, eschar	Recovered
137	245	0.05	—	—	Marked edema, lysis, rupture of skin, eschar	Recovered
135	255	1	A	0.001	Moderate edema, lysis	Dead in 24 hours
119	255	1	B	0.001	Edema, lysis, eschar	Recovered
131	240	1	C	0.01	Edema	Dead in 3 days*
128	220	1	D	0.001	Moderate edema	Dead in 24 hours
126	245	1	E	0.001	Edema, no lysis	Dead in 48 hours
125	240	1	F	0.01	None	Lived‡
129	215	1	G	0.001	Edema, lysis, eschar	Recovered

*Confirming result in Experiment 3.
‡Not confirming result in Experiment 3.

Experiment 3. November 4, 1942, a series of guinea pigs was injected with mixtures of 1 cubic centimeter of toxin and 0.01 cubic centimeter of each of the antitoxins, along with the usual controls. The data are summarized in Table III.

Table III shows that the test dose of 1 cubic centimeter killed a large normal guinea pig in about 40 hours. Guinea pigs receiving smaller doses down to 0.05 cubic centimeter all showed characteristic lesions but recovered.

Five of those receiving mixtures of 1 cubic centimeter of toxin and 0.01 cubic centimeter of antitoxin showed no result, but in 2 instances this dose of antitoxin failed to protect against the development of the usual lesions; 1 of these guinea pigs died on the 5th day but the other one recovered slowly.

Experiment 4. November 19, 1942, a series of guinea pigs was injected with mixtures of 1 cubic centimeter and 0.001 cubic centimeter of antitoxin, except that in the case of antitoxins C and F, 0.01 cubic centimeter was used to recheck the results in Experiment 3. The usual controls were used. The results are shown in Table IV.

TABLE V.—SUMMARY OF EXPERIMENTS 1 TO 4 ON PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST TOXIN OF BACILLUS PERFRINGENS

Number of guinea pigs	Average weight of guinea pigs	Dose of toxin in 1 c.c.	Serum	Dose of serum in 1 c.c.	Lesions	Died	Lived
4	378	1	—	—	Typical	3	1*
2	342	0.5	—	—	Typical	1‡	1
2	337	0.25	—	—	Typical	—	2
2	342	0.2	—	—	Typical	1‡	1
2	330	0.125	—	—	Typical	2‡	—
2	325	0.1	—	—	Typical	—	2
2	305	0.05	—	—	Typical	—	2
1	315	1	A	1	None	—	1
1	335	1		0.1	None	—	1
1	365	1		0.01	None	—	1
1	255	1		0.001	Typical	1	—
1	315	1	B	1	None	—	1
1	340	1		0.1	None	—	1
1	365	1		0.01	None	—	1
1	255	1		0.001	Typical	—	1
1	310	1	C	1	None	—	1
1	330	1		0.1	None	—	1
2	297	1		0.01	Typical	2	—
1	310	1	D	1	None	—	1
1	330	1		0.1	None	—	1
1	345	1		0.01	None	—	1
1	220	1		0.001	Typical	1	—
1	310	1	E	1	None	—	1
1	320	1		0.1	None	—	1
1	345	1		0.01	None	—	1
1	245	1		0.001	Typical	1	—
1	300	1	F	1	None	—	1
1	320	1		0.1	None	—	1
1	330	1		0.01	Typical	—	1
1	240	1		0.01	None	—	1
1	215	1	G	1	None	—	1
1	305	1		0.1	None	—	1
1	315	1		0.01	None	—	1
1	215	1		0.001	Typical	—	1

*Survival attributed to early rupture of skin.
‡Deaths occurred on 14th, 18th, 10th and 11th days, probably due to secondary infections of adherent eschars.

Table IV shows that all 5 of these serums tested for prophylactic action in a dose of 0.001 cubic centimeter failed to protect guinea pigs against 1 cubic centimeter of Bacillus perfringens toxin. Of the two serums which failed in Experiment 3 to protect in a dose of 0.01 cubic centimeter, serum C failed again here, confirming the earlier result, while serum F protected fully, disagreeing with the result in Experiment 3. Serum F should have been tested in a dose of 0.001 cubic centimeter but this was not done.

The results of Experiments 1 to 4 are combined and summarized in Table V.

Table V shows that 1 cubic centimeter of Bacillus perfringens toxin killed 3 of 4 control guinea pigs, 2 within 22 and 40 hours, respectively, 1 in 5 days. One animal in which early rupture of the skin occurred survived and the lesion healed completely in about 7 weeks. Of 2 control animals receiving 0.5 cubic centimeter of toxin one recovered; the other developed an adherent eschar which became secondarily infected, resulting in death in 14 days. Similar accidents occurred in 3 guinea pigs receiving 0.2 and 0.125 cubic centimeter of toxin while a total of 8 control guinea pigs receiving doses of from 0.05 to 0.5 cubic centimeter showed the typical early edema and lysis followed by loss of fluid either by rupture of the skin or by slow leakage and absorption, formation of eschars, granulation, and complete healing in 6 to 8 weeks. In evaluating these controls, emphasis is placed upon the characteristic lesions produced by the toxin during the first 24 hours rather than upon death or survival of the animals then or later as these terminal events are so dependent upon uncontrollable accidents, such as early rupture of the skin or later secondary infections of the large adherent eschars which always form if the animal survives the earlier effects of the toxin.

Five of the 7 brands of antitoxin tested gave complete protection against 1 cubic centimeter of this toxin in doses of 0.01 cubic centimeter or larger. All 5 failed in a dose of 0.001 cubic centimeter. Two which gave complete protection in a dose of 0.1 cubic centimeter failed at 0.01 cubic centimeter but one of these gave complete protection at 0.01 cubic centimeter when retested later; these 2 were not tested at 0.001 cubic centimeter for lack of time.

EXPERIMENTS WITH LIVING CULTURES OF BACILLUS PERFRINGENS

Experiment 5. January 8, 1943, a series of guinea pigs was used to test both the prophylactic and therapeutic action of serum B against a virulent culture of Bacillus perfringens. The culture selected was my old "Bacillus welchii," No. 36, which was isolated in 1918 from a swelled can of commercially canned Swiss chard (4). This culture has been maintained ever since in deep brain medium or deep 1 per cent agar at room temperature and has retained its originally high virulence remarkably well, having never failed in all these 25 years to kill overnight guinea pigs with typical lesions, in a dose of 1 cubic centimeter or less. It always produces a massive edema on subcutaneous injection followed very soon by extensive spreading, lysis, emphysema, and death within 18 to 24 hours. It belongs to Wilsdon's type A (1).

One cubic centimeter of a 16 hour culture of Bacillus perfringens No. 15196 (old No. 36) in glucose broth in a constricted tube with marble seal (5) was injected into each of 10 guinea pigs during an interval of 12 minutes. The heaviest animal received no treatment; it died in exactly 6 hours; on autopsy the characteristic emphysema and lysis were seen. A culture from the heart's blood was sterile. The lightest animal received 1 cubic centimeter of serum B simultaneously; at 6 hours there was a slight edema which subsided overnight. It survived without any visible effect. The remainder of these guinea pigs were injected subcutaneously at intervals up to 6 hours with 1 cubic centimeter or 4 cubic centimeters of serum B as indicated in the following protocol.

Guinea pig No. 150; weight, 330 grams; received 1 cubic centimeter of culture, subcutaneously. No treatment was given. Subcutaneous emphysema and lysis were present but heart's blood was sterile. Animal died at 6 hours.

Guinea pig No. 149; weight, 235 grams; received 1 cubic centimeter of serum simultaneously. At 6 hours there was slight edema which subsided next day. Lived.

Guinea pig No. 156; weight, 245 grams. At 1 hour there was slight edema, and 1 cubic centimeter of serum was given subcutaneously; at 6 hours, slight edema; at 24 hours, a sore and fluctuating area, 4 by 5 centimeters, was noted, but animal apparently was not sick; at 48 hours, the fluctuating area was drying up; at 72 hours, weight was 225 grams, and necrotic eschar was 5 centimeters in diameter; at 11 days, a dry adherent scab 3 centimeters in diameter was present. Lived.

Guinea pig No. 148; weight 280 grams. At 1 hour there was slight edema, and 4 cubic centimeters of serum was given subcutaneously; at 6 hours, slight edema; at 24 hours, slight necrosis; at 48 hours, the edema was drying up; at 72 hours, the dry area of necrosis was 1 centimeter across; at 11 days, no lesions were noted. Lived.

Guinea pig No. 155; weight 300 grams. At 2 hours there was slight edema, and 1 cubic centimeter of serum was given subcutaneously; at 6 hours, moderate edema; at 24 hours, not ill; area of liquefaction and necrosis measured 1 by 2 centimeters; at 48 hours, area of necrosis drying up; at 72 hours, small dry area of necrosis 1 by 2 centimeters; at 11 days, about the same. Lived.

Guinea pig No. 154; weight 305 grams. At 2 hours, there was slight edema, and 4 cubic centimeters of serum was given subcutaneously; at 6 hours, moderate edema; at 24 hours, animal was not ill, area of liquefaction and necrosis measured 2 by 3 centimeters; at 48 hours, area of necrosis was drying up; at 72 hours, dry area of necrosis was 1 centimeter across; at 11 days, about the same. Lived.

Guinea pig No. 137; weight 305 grams. At 3 hours there was slight edema, and 1 cubic centimeter of serum was given subcutaneously; at 6 hours, moderate edema; at 24 hours, not ill, area of necrosis was 2 by 3 centimeters; at 48 hours, area of necrosis drying up; at 11 days, dry adherent eschar 2 by 3 centimeters. Lived.

Guinea pig No. 145; weight 315 grams. At 3 hours there was slight edema, 4 cubic centimeters of serum was given subcutaneously; at 6 hours, moderate edema; at 24 hours, not ill, area of necrosis 2 by 3 centimeters was drying up; at 48 hours, dry area of necrosis 2 by 3 centimeters; at 11 days, dry adherent eschar 2 by 3 centimeters. Lived.

Guinea pig No. 152; weight 335 grams. At 6 hours moderate edema and emphysema were noted. One cubic centimeter of serum was given subcutaneously. At 24 hours, there was present a marked edematous area 4.5 centimeters by 7 centimeters with a small area of lysis 2 centimeters across. The area was painful but animal apparently was not sick; at 48 hours, about the same; at 72 hours, two areas of lysis were noted, each 3.5 centimeters across and connected by sinus, fluctuating, moist and painful; at 96 hours, weight 335 grams, areas dry; at 11 days, granulating area 2 centimeters by 3 centimeters. Lived.

Guinea pig No. 153; weight, 365 grams. At 6 hours, marked edema, emphysema, and lysis were noted. Four cubic centimeters of serum were given subcutaneously. At 24 hours, area of lysis 4.5 centimeters by 7 centimeters, painful but animal apparently not sick; at 48 hours, fluctuating area 3 centimeters deep, 5 centimeters by 5 centimeters, sore but not sick; at 72 hours, about the same, some absorp-

TABLE VI.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST BACILLUS SEPTICUS

Dose of culture 1 c.c. Dose of antitoxin 1 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum* in c.c.	Lesions	Final result
76	350	1	—	—	Typical	Dead in 16 hours
77	350	0.1	—	—	Typical	Dead in 20 hours‡
78	350	0.01	—	—	None	Lived
75	300	0.001	—	—	None	Lived
71	288	1	A	1	None	Lived
64	280	1	B	1	Delayed	Dead in 5 days‡
63	282	1	C	1	None	Lived
69	285	1	D	1	None	Lived
62	282	1	E	1	Typical	Dead in 18 hours‡
65	275	1	F	1	None	Lived
56	210	1	G	1	None	Lived

*1 week previously with 1 c.c. Bacillus perfringens toxin.
‡Heart's blood showed pure culture of Bacillus septicus.

tion, no rupture of skin; at 96 hours, about the same, weight 340 grams; at 11 days, clean granulating area 4 centimeters over chest wall, healing. Lived.

It is clear from these data that serum B had not only prophylactic but marked therapeutic action against infection with Bacillus perfringens, saving the lives of all treated animals, in 2 of which treatment was not started until the control animal was already dead.

EXPERIMENT ON BACILLUS SEPTICUS

In order to utilize the animals surviving Experiments 1 and 2 on Bacillus perfringens, these were tested for passive immunity to Bacillus septicus. The culture used for this experiment was my No. 2397A which was received in September, 1928, from Dr. J. P. Scott of Kansas State College, Manhattan, Kansas, as Robertson's "Vibrion septique, No. 282 N. I. F., Type 2, Lister Institute 1923."

Experiment 6. October 8, 1942, a series of guinea pigs was injected subcutaneously with Bacillus septicus No. 2397A grown for 24 hours in a 1 per cent glucose meat broth medium, in the doses which are indicated in Table VI.

The control animals were all fresh and unused prior to this test; the test animals had all received freshly made mixtures of 1 cubic centimeter of the indicated antitoxins with 1 cubic centimeter of the toxin of Bacillus perfringens in Experiment 1 a week previously. Six of these had shown no symptoms whatever but one, guinea pig No. 56, had had a slight transient edema.

The results are shown in Table VI.

Table VI shows that Bacillus septicus killed large guinea pigs in a dose of 0.1 cubic centimeter in about 20 hours, while 0.01 cubic centimeter had no apparent effect. Those animals which died showed the postmortem subcutaneous and pulmonary congestion, edema and slight emphysema so characteristic of animals dying with infection by Bacillus septicus. The heart's blood yielded pure cultures of Bacillus septicus and the characteristic filaments were demonstrated in every instance upon the surfaces of the livers.

Five of the animals injected with 1 cubic centimeter of the different gas gangrene serums a week previously were still protected completely against a dose of culture ten times as large, showing no lesions of any kind and surviving.

One animal which had received serum B was apparently well on the 4th day but was found dead on the 5th day with characteristic lesions and a pure culture of Bacillus septicus in the heart's blood. Another, which had received serum E, died along with the controls in about 18 hours with similarly characteristic postmortem findings.

Experiment 7. October 30, 1942 a similar experiment was made with the guinea pigs used in Experiment 2 as test animals. These had received freshly made mixtures of 0.1 cubic centimeter of the various serums with 1 cubic centimeter of Bacillus perfringens toxin one week previously and had shown no symptoms. All other conditions were the same except that a 48 hour meat-broth culture of Bacillus septicus 2397A was used. The results are shown in Table VII.

Table VII shows that 0.1 cubic centimeter of the test culture of Bacillus septicus killed a guinea pig in about 24 hours while 0.01 cubic centimeter had no apparent effect.

TABLE VII.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST BACILLUS SEPTICUS

Dose of culture 1 c.c. Dose of antitoxin 0.1 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum* in c.c.	Lesions	Final result
99	330	1	—	—	Typical	Dead in 20 hours‡
97	295	0.1	—	—	Typical	Dead in 24 hours‡
107	275	0.01	—	—	None	Lived
92	325	1	A	0.1	Typical	Dead in 20 hours‡
90	325	1	B	0.1	Delayed	Dead in 36 hours‡
86	335	1	C	0.1	None	Lived
93	295	1	D	0.1	Typical	Dead in 20 hours‡
88	320	1	E	0.1	Typical	Dead in 20 hours‡
94	315	1	F	0.1	Typical	Dead in 20 hours‡
91	305	1	G	0.1	None	Lived

*1 week previously with 1 c.c. Bacillus perfringens toxin.
‡Heart's blood showed pure culture of Bacillus septicus.

TABLE VIII.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST BACILLUS SEPTICUS

Dose of culture 1 c.c. Dose of antitoxin 0.01 c.c.

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Serum	Dose of serum in c.c.*	Lesions	Final result
96	450	1	—	—	Typical	Dead in 17 hours†
115	315	0.1	—	—	Typical	Dead in 21 hours†
109	295	0.01	—	—	None	Lived
114	430	1	A	0.01	Typical	Dead in 17 hours†
123	395	1	B	0.01	Typical	Dead in 17 hours†
120	370	1	C	0.01	Typical	Dead in 17 hours†
124	365	1	D	0.01	Typical	Dead in 17 hours†
121	340	1	E	0.01	Typical	Dead in 17 hours†
118‡	290	1	F	0.01	Typical	Dead in 20 hours

*6 days previously with 1 c.c. Bacillus perfringens toxin.
†Heart's blood showed pure culture of Bacillus septicus.
‡This animal had large clean eschar on belly; no pulmonary congestion at autopsy; heart's blood cultures sterile.

Four of the animals that had been protected against Bacillus perfringens with 0.1 cubic centimeter of antitoxin died in about the same time as the control which received the same amount, i.e., 1 cubic centimeter of culture; 1 died in about 36 hours. All of the animals that died showed the characteristic pathologic changes aforementioned and yielded pure cultures of Bacillus septicus in culture from the heart's blood.

Two animals, which had been inoculated with serums C and G, showed no symptoms and survived.

Experiment 8. November 10, 1942, the guinea pigs which had received 0.01 cubic centimeter of the different antitoxic serums along with 1 cubic centimeter of Bacillus perfringens toxin 6 days previously were used. One of these animals still had a large but clean eschar. Serum G was not represented, the corresponding animal having died in Experiment 3. A 24 hour glucose broth culture of Bacillus septicus 2397A grown in a constricted tube (5) was used as the test culture. The results are shown in Table VIII.

Table VIII shows that only one animal in this experiment survived, i.e. the control which received only 0.01 cubic centimeter of culture. The first control and all but one of the test animals were found dead in 17 hours. The second control, guinea pig No. 115, and guinea pig No. 118 died in 21 and 20 hours, respectively.

All of those that died excepting No. 118 showed the usual pathogenic changes and positive heart's blood cultures. No. 118 was the one which had a large healing eschar resulting from its prior injection with Bacillus perfringens toxin. This animal died in 20 hours but showed only a moderate subcutaneous edema and no marked congestion either of the subcutaneous tissues or of the lungs, and its heart's blood culture was negative. The observations suggest a possibly adjuvant action.

Experiments 6, 7, and 8 are combined in Table IX.

It would not be fair to compare the summary of experiments on Bacillus septicus culture with that on Bacillus perfringens toxin, owing to the diversity of factors involved, such as the use of whole culture instead of toxin and the lapse of a week's time from the injection of the antitoxin before the cultures were injected. Therefore, while a

TABLE IX.—SUMMARY OF EXPERIMENTS 6, 7, AND 8 ON PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN AGAINST BACILLUS SEPTICUS

Number of guinea pigs	Average weight of guinea pigs	Dose of toxin in 1 c.c.	Serum	Dose of serum in 1 c.c.	Lesions	Died	Lived
3	377	1	—	—	Typical	3	—
3	330	0.1	—	—	Typical	3	—
3	290	0.01	—	—	None	—	3
1	288	1	A	1	None	—	1
1	325	1		0.1	Typical	1	—
1	305	1		0.01	Typical	1	—
1	280	1	B	1	Delayed	1	—
1	325	1		0.1	Delayed	1	—
1	305	1		0.01	Typical	1	—
1	282	1	C	1	None	—	1
1	335	1		0.1	None	—	1
1	370	1		0.01	Typical	1	—
1	285	1	D	1	None	—	1
1	295	1		0.1	Typical	1	—
1	365	1		0.01	Typical	1	—
1	282	1	E	1	Typical	1	—
1	320	1		0.1	Typical	1	—
1	340	1		0.01	Typical	1	—
1	275	1	F	1	None	—	1
1	315	1		0.1	Typical	1	—
1	340	1		0.01	Typical	1	—
1	210	1	G	1	None	—	1
1	305	1		0.1	None	—	1

higher percentage of animals injected with Bacillus septicus died in spite of prior injections of antitoxin it is not possible to conclude that these serums had less protective action against Bacillus septicus than against Bacillus perfringens. The important conclusion seems to be that all but one serum had marked protective action against at least 10 fatal doses of culture when given a week previously in a dose of 1 cubic centimeter and in 2 instances in a dose of 0.1 cubic centimeter. Two serums, B and E, apparently had slight protective power under these conditions, but the next experiment showed that one of these, B, was by no means devoid of prophylactic value.

One notable difference in the action of Bacillus septicus and Bacillus perfringens is to be noted. Guinea pigs frequently survive and recover perfectly after having severe lesions from either the toxin or culture of Bacillus perfringens but they rarely do so after an injection of Bacillus septicus which produces noticeable lesions. Furthermore, guinea pigs inoculated with small doses of Bacillus septicus often show no signs of illness at all for a day or so but succumb rapidly once infection, that is, septicemia, really starts. In this respect an infection with Bacillus septicus resembles an infection with Bacillus anthracis.

Experiment 9. January 9, 1943, a series of guinea pigs was used to test the prophylactic and therapeutic value of serum B against Bacillus septicus. Upon analyzing the data already collected, we later realized that this was really one of the two least favorable samples of antitoxin available for such an experiment. It was intended to extend these tests to all of the other serums, but this was impossible because of the limitations of time.

Each of 12 normal guinea pigs was injected subcutaneously in an interval of 13 minutes with 1 cubic centimeter of a glucose broth culture of Bacillus septicus 2397A grown for 3 days in a constricted tube with marble seal (5). Three served as untreated controls on dosage; 2 of these died in 23 hours, 1 in 48 hours, all with typical pathology and positive heart's blood cultures. One received 1 cubic centimeter of serum B simultaneously; it never showed any symptoms. The others were treated at intervals by subcutaneous injection of 1 or 4 cubic centimeter of serum B as indicated in the following protocol, with the results noted.

Guinea pig No. 168; weight 370 grams. One cubic centimeter of culture was given subcutaneously. Animal was dead in 23 hours.

Guinea pig No. 157; weight 350 grams. One tenth cubic centimeter of culture was given subcutaneously. Animal was dead in 23 hours.

Guinea pig No. 151; weight 340 grams. One-hundredth cubic centimeter of culture was given subcutaneously. At 23 hours, there was slight subcutaneous edema. Animal was not sick. It was dead in 48 hours.

Guinea pig No. 162; weight 220 grams. One cubic centimeter of culture plus 1 cubic centimeter of serum B were given subcutaneously. No result. Lived.

Guinea pig No. 166; weight 250 grams. One cubic centimeter of culture was given subcutaneously. At 2

hours, there was slight edema, 1 cubic centimeter of serum B was given subcutaneously at 25 hours, slight edema, not sick; at 48 hours, dry necrotic area 1 centimeter across. Lived.

Guinea pig No. 158; weight 255 grams. One cubic centimeter of culture was given subcutaneously. At 2 hours, slight edema, 4 cubic centimeters of serum B were given subcutaneously; at 23 hours, slight edema, not sick; at 48 hours, dry necrotic area 1.5 centimeter across. Lived.

Guinea pig No. 159; weight 290 grams. One cubic centimeter of culture was given subcutaneously. At 4 hours, 20 minutes, slight edema. One cubic centimeter of serum B was given subcutaneously; at 23 hours, slight edema, not sick. Animal was dead in 47 hours.

Guinea pig No. 160; weight 300 grams. One cubic centimeter of culture was given subcutaneously. At 4 hours, 20 minutes, slight edema, 4 cubic centimeters of serum B was given subcutaneously. Animal was dead in 23 hours.

Guinea pig No. 164; weight 310 grams. One cubic centimeter of culture was given subcutaneously. At 7.5 hours, moderate edema. One cubic centimeter of serum B was given subcutaneously. Animal was dead in 23 hours.

Guinea pig No. 167; weight 310 grams. One cubic centimeter of culture was given subcutaneously. At 7.5 hours, moderate edema. Four cubic centimeters of serum B were given subcutaneously. Animal was dead in 23 hours.

Guinea pig No. 161; weight 320 grams. One cubic centimeter of culture was given subcutaneously. At 12 hours, marked edema, 1 cubic centimeter of serum B was given subcutaneously. Animal was dead in 23 hours.

Guinea pig No. 165; weight 330 grams. One cubic centimeter of culture was given subcutaneously. At 12 hours, marked edema, 1 cubic centimeter of serum B was given subcutaneously. Animal was dead in 23 hours.

All animals that died showed the usual pathologic picture on autopsy and all heart blood cultures yielded Bacillus septicus.

The results showed that serum B had definite prophylactic but little therapeutic value under the conditions imposed. Unfortunately it was not possible to repeat this experiment with weaker test doses which the writer believes would have given more favorable results, or to test the therapeutic action of the other brands of serum, some of which might well have given much better results.

EXPERIMENTS ON BACILLUS NOVYI

For these experiments my Bacillus novyi No. 15197 (old No. 140) was selected. This culture was received from Dr. Michel Weinberg of the Pasteur Institute in Paris, France, in March, 1921, as Bacillus oedematiens No. 128. Without entering upon a discussion of the long controversy over the correct name of this organism, let us say simply that we regard Bacillus novyi as the earliest valid binomial for this species (4).

TABLE X.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN B AGAINST BACILLUS NOVYI

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Dose of serum in c.c.	Lesions	Final result
207	280	1	—	Typical	Dead in 22 hours*
202	270	0.1	—	Typical	Dead in 22 hours*
205	260	0.01	—	Typical	Dead in 26 hours*
206	260	0.001	—	Typical	Recovered
204	235	1	1	None	Lived
209	225	1	0.1	None	Lived
203	205	1	0.01	Typical	Dead in 22 hours‡
201	200	1	0.001	Typical	Dead in 22 hours*

*Heart's blood culture negative.
‡No culture made from heart's blood.

Owing to the increased number of infections by Bacillus novyi encountered during the African campaign (9) the inclusion of antitoxin for Bacillus novyi in polyvalent anaerobic gas gangrene serum suddenly became a matter of considerable urgency. However, serum B was the only one claiming to contain antibodies for this species at the time these experiments were in progress. Two experiments were conducted with this serum.

Experiment 10. February 25, 1943, a series of guinea pigs was injected with Bacillus novyi 15197 grown for 3 days in glucose broth in a constricted tube with marble seal (5). Four animals served as controls on dosage while 4 others comprised the test with serum B given simultaneously. The results are shown in Table X.

Table X shows that 1 cubic centimeter of this culture of Bacillus novyi killed small guinea pigs in about 22 hours. One-hundredth cubic centimeter killed one in about 46 hours with typical pathologic changes, but while 0.001 cubic centimeter produced a marked anasarca this gradually subsided without rup-

ture of the skin and this animal slowly recovered.

On the other hand guinea pigs receiving 1 cubic centimeter and 0.1 cubic centimeter of serum simultaneously with 1 cubic centimeter of culture showed no symptoms at all and lived, but those receiving doses of 0.01 cubic centimeter and 0.001 cubic centimeter died about the same time as the controls. Cultures were made from the heart's blood of 4 of the animals that died but all were negative.

PROPHYLACTIC AND THERAPEUTIC ACTION OF SERUM B AGAINST BACILLUS NOVYI

Experiment 11. March 5, 1943, a series of 11 guinea pigs was injected subcutaneously during a period of 35 minutes with Bacillus novyi 15197 grown for 48 hours in glucose broth in a constricted tube with marble seal (5).

Three animals served as controls on dosage, 2 as prophylactic controls on the serum. The details of treatment with serum B and the results are shown in the following protocol.

Controls on Dosage

Guinea pig No. 142; weight 505 grams; 0.1 cubic centimeter of culture was given subcutaneously. At 24 hours, there was moderate edema. Animal was dead in 27 hours.

Guinea pig No. 198; weight 450 grams; 0.01 cubic centimeter of culture was given subcutaneously. At 24 hours, moderate edema was noted. Animal was dead in 48 hours.

Guinea pig No. 176; weight 430 grams; 0.001 cubic centimeter of culture was given subcutaneously. At 24, 48, and 72 hours, slight edema was noted. Animal recovered.

Controls on Serum

Guinea pig No. 210; weight 210 grams; 0.01 cubic centimeter of culture plus 0.01 cubic centimeter of serum was given subcutaneously, no results. Lived.

Guinea pig No. 191; weight 370 grams; 0.01 cubic centimeter of culture plus 0.001 cubic centimeter of serum were given subcutaneously, no results. Lived.

Tests on Therapeutic Action of Serum

Guinea pig No. 186; weight 365 grams; 0.01 cubic centimeter of culture was given subcutaneously. At 2 hours, no symptoms, 1 cubic centimeter of serum was given subcutaneously; at 24 hours, moderate edema; at 48 hours, edema subsiding; at 72 hours, edema almost gone, no break in skin; at 6 days, completely recovered. Lived.

Guinea pig No. 194: weight 350 grams: 0.01 cubic centimeter of culture was given subcutaneously. At 4 hours, slight edema, 1 cubic centimeter of serum was given subcutaneously; at 24 hours, moderate edema; at 48 hours, edema subsiding; at 96 hours, edema almost gone; at 6 days, completely recovered. Lived.

Guinea pig No. 190; weight 330 grams; 0.01 cubic centimeter of culture was given subcutaneously. At 6 hours, slight edema, 1 cubic centimeter of serum was given subcutaneously; at 24 and 48 hours, moderate edema; at 72 hours and 96 hours, severe edema; at 120 hours, found dead (pneumonia). Died.

Guinea pig No. 189; weight 310 grams; 0.01 cubic centimeter of culture was given subcutaneously. At 8 hours, slight edema, 1 cubic centimeter of serum was given subcutaneously; at 24 hours and 48 hours moderate edema; at 72 hours, edema subsiding; at 96 hours, completely recovered. Lived.

Guinea pig No. 195; weight 305 grams; 0.01 cubic centimeter of culture was given subcutaneously. At 24 hours, moderate edema, 1 cubic centimeter of serum was given subcutaneously; at 48 and 72 hours, severe edema, oozing; at 96 hours, severe edema, skin ruptured; at 11 days, adherent eschar, 1 centimeter by 3 centimeter with considerable adjacent edema, animal losing weight and in poor condition; at 20 days, eschar clean, granulating; at 24 days, eschar clean, 1.5 centimeter by 3 centimeter; at 54 days, completely recovered. Lived.

Guinea pig No. 199; weight 300 grams; 0.01 cubic centimeter of culture was given subcutaneously. At 24 hours, moderate edema; at 27 hours, severe edema. 1 cubic centimeter of serum was given subcutaneously; at 54 days, completely recovered. Lived.

All animals that died were examined postmortem. The characteristic moderate to marked subcutaneous edema was observed in each instance. There was some blood tinged effusion but little or no true congestion and no emphysema or lysis. The lungs were pale except in the case of guinea pig No. 190 which showed a moderate congestion of all lobes indicating pneumonia. There were no other gross changes in the viscera. Heart blood cultures were made in each case but all were negative.

This experiment showed that gas gangrene serum B had considerable therapeutic action in guinea pigs inoculated with a small but fatal dose of Bacillus novyi, if used within 24 hours.

EXPERIMENTS ON BACILLUS HISTOLYTICUS

Serum B was the only one that claimed to have antibodies for Bacillus histolyticus. The culture selected for the following tests was

TABLE XI.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN B AGAINST BACILLUS HISTOLYTICUS

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Dose of serum in c.c.	Lesions	Final result
98	610	1	—	Typical	Dead in 16 hours
103	530	0.1	—	Typical	Dead in 40 hours
107	475	1	1	None	Lived
110	440	1	0.1	Slight edema	Lived
101	435	1	0.01	Typical	Dead in 16 hours
109	390	1	0.001	Typical	Dead in 16 hours

TABLE XII.—PROTECTIVE ACTION OF GAS GANGRENE ANTITOXIN B AGAINST BACILLUS SORDELLII

Guinea pig number	Weight in grams	Dose of toxin in c.c.	Dose of serum in c.c.	Lesions	Final result
137	700	1	—	Typical	Dead in 18 hours
66	590	0.1	—	Typical	Dead in 18 hours
73	635	0.01	—	Typical	Dead in 42 hours
122	600	0.001	—	Typical	Dead in 42 hours
68	565	1	1	Slight transient edema	Lived

No. 12597 which was isolated in August 1940 from a culture submitted by Captain D. M. Kuhns from a fatal case of gaseous gangrene at Letterman General Hospital, San Francisco, California. The original culture was contaminated by Bacillus sporogenes and Micrococcus epidermidis.

Experiment 12. December 9, 1942, a series of guinea pigs was injected subcutaneously with a pure culture of Bacillus histolyticus No. 12597 grown for 24 hours in a glucose-meat-broth medium. Two of these animals served as controls while 4 received also varying amounts of serum B simultaneously as shown in Table XI.

Table XI shows that serum B protected a guinea pig against at least 10 fatal doses of Bacillus histolyticus culture which was inoculated subcutaneously. The marginal animal showed a slight transient edema but there was no lysis.

Although guinea pigs inoculated with Bacillus histolyticus subcutaneously generally show a striking and peculiar denudation of skin at the site of inoculation, they usually do not die. But both guinea pigs used as controls in this experiment did so.

Control 98 which received 1 cubic centimeter of culture, showed at 15 hours an area 3 centimeters across completely denuded of skin and was obviously sick. It died at 16 hours at which time an area 7 by 11 centimeters was denuded but there was no perforation of the peritoneum and all of the viscera was normal in appearance. A culture from the heart's blood was sterile.

Control 103 which received 0.1 cubic centimeter also showed at 15 hours an area about 3 centimeters across denuded of skin but this animal was apparently not sick. However, at 40 hours it was found dead with an abdominal perforation and its intestines hanging out, which is common in animals receiving intramuscular injections of Bacillus histolyticus. The Bacillus histolyticus was recovered from the heart's blood.

Guinea pigs Nos. 101 and 109 both developed large areas (6 by 10 cm.) of denudation without perforation at death; cultures from the heart's blood were negative in both cases.

PRELIMINARY EXPERIMENTS ON BACILLUS SORDELLII

Serum B was the only serum claiming to have antibodies for Bacillus sordellii.

Experiment 13. For this experiment my strain No. 1316 was selected. This strain was received in 1927 from Dr. Frank L. Meleney of Presbyterian Hospital, New York, as "C. edematoides No. 1, isolated from patient" (10). Its identity with the previously named Bacillus sordellii was shown both by Humphreys and Meleney (8) and by Hall, Jungherr, and Rymer (6, 7).

Five guinea pigs were inoculated subcutaneously with a 48 hour meat broth culture as indicated in Table XII.

Table XII shows that 1 cubic centimeter of serum B protected a large guinea pig against at least 1000 fatal doses of Bacillus sordellii culture. This animal showed only a slight transient edema.

The controls all died showing the massive edema which characterizes infection and intoxication by this highly pathogenic species, and the heart's blood yielded pure cultures of Bacillus sordellii in every instance except guinea pig No. 122 which was negative.

Unfortunately it was not possible to extend the experiments to the limit of protective action of this serum or to determine it possible therapeutic value.

SUMMARY

Seven brands of gas gangrene antitoxin were examined. Six of these were bivalent and were labelled to contain 10,000 units each of Bacillus perfringens and Bacillus septicus antitoxins. One was pentavalent and labelled to contain in addition 3000 units of Bacillus histolyticus antitoxin and 1,500 units each of Bacillus novyi and Bacillus sordellii antitoxins. It is pointed out that, owing to discrepancies in the size of the international units for different antitoxins and in spite of the smaller indicated unitage, this serum was heavily overloaded with Bacillus novyi and Bacillus sordellii antitoxins.

All of these antitoxins were first tested against a weak toxin of Bacillus perfringens which generally killed guinea pigs in a dose of 1 cubic centimeter but still produced marked lesions in a dose of 0.05 cubic centimeter.

Five of the 7 brands of serum gave complete prophylactic protection against 1 cubic centimeter of this toxin in doses of 0.01 cubic centimeter or larger; all 5 failed in a dose of 0.001 cubic centimeter. One gave complete protection in a dose of 0.1 cubic centimeter but failed at 0.01 cubic centimeter while another gave complete protection at 0.1 cubic centimeter and failed irregularly at 0.01 cubic centimeter.

The pentavalent serum was shown to have not only prophylactic but marked therapeutic action against infections in guinea pigs with a virulent culture of Bacillus perfringens, saving the lives of all animals treated within 6 hours when the untreated control was already dead. It seems quite certain that all of the guinea pigs in this series would have died within a few hours if they had not been treated with serum.

The immunity conferred by 1 cubic centimeter of 5 antitoxins injected along with 1 cubic centimeter of Bacillus perfringens was shown to persist for at least a week when challenged with at least 10 lethal doses of Bacillus septicus culture while in one instance there was partial persistence and in one case none at all. Two serums injected in a dose of 0.1 cubic centimeter along with 1 cubic centimeter of Bacillus perfringens toxin still protected against Bacillus septicus after a week but all of the rest failed.

The pentavalent serum, which was one of the two weakest serums against Bacillus septicus in the preceding tests, was tried out both prophylactically and therapeutically. It was shown to have definite prophylactic value but no therapeutic value after 2 hours under the severe conditions imposed.

This same serum was shown to have prophylactic values in a dose of 0.1 cubic centimeter and therapeutic values in a dose of 1 cubic centimeter at 27 hours against at least 100 lethal doses of Bacillus novyi. It had prophylactic values in a dose of 0.1 cubic centimeter against at least 10 lethal doses of Bacillus histolyticus and in a dose of 1 cubic centimeter saved the life of a guinea pig given at least 1000 lethal doses of Bacillus sordellii.

Further experiments are indicated to extend these findings on the therapeutic action of this serum to the other brands and with small more slowly acting infecting doses to show that these serums do have effective therapeutic values when properly used as an adjunct to surgery.

CONCLUSION

There is no reason to doubt the prophylactic value of seven American gas gangrene antitoxins against the anaerobic infections for which they were intended. One of these serums has been shown to have marked therapeutic values against Bacillus perfringens and Bacillus novyi but only slight therapeutic value against Bacillus septicus under the conditions of a possibly too severe test. A pattern for such studies has been established which should be extended under conditions more favorable to a successful demonstration, that is, with smaller and more slowly acting doses of cultures.

It is believed that the principal value of gas gangrene antitoxin is prophylactic, to prevent or delay anaerobic infections until adequate surgery can be secured, but that it also has definite though limited therapeutic value as an adjunct to surgery in the treatment of malignant edema and gaseous gangrene in man.

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STUDY OF THE LATE SYMPTOMS OF CASES OF IMMERSION FOOT

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DURING the early part of February, 1943, there were admitted to the hospital at this post a number of patients with immersion foot, incurred as a result of the sinking of the patients' transport. The condition varied from mild to severe, and the patients were treated in two main groups, as follows: In the first group the legs were exposed to fairly cool air, under cradles. In the second group the legs were wrapped loosely in sterile cotton. Both groups were further treated by bed rest.

A small third group, made up mainly of civilians, contractors' employees, and merchant marines, whose going and coming in the hospital could not be completely controlled due to the large number of cases and general confusion, undertook a type of treatment of their own; namely, Finnish type steam baths. These patients made a much more rapid clearing of local and general symptoms than did the group treated with bed rest and cooling. It is felt that this type of treatment should have further investigation.

After the discharge to duty of the Army patients, and as time went on, it was noticed that a number were having persistent symptoms referable to their lower extremities. This persistence of symptoms was noticed first among mess personnel in the hospital, whose duties required long periods of standing on their feet. Inquiry then showed (about 14 months after onset) that a considerable number of the men who were on the sunken boat, whether they had been hospital patients at the original onset or not, and who were still on duty at this post, had persistent complaints of one type or another referable to their lower extremities.

It was then determined to carry out the present study of personnel remaining at the post at the present time, with the following findings:

General. Of the 65 persons remaining at this post in April, 1944, 14 months after the sinking, it was found that 49, or 75 per cent, of the total group had complaints referable to their lower extremities; and that of these 49 patients examined, 42 had abnormal physical findings in their legs or feet, which was 64 per cent of the total group remaining, or 85 per cent of these presenting complaints.

These men were of various commissioned and enlisted grades, and all branches of service in the Army. Their ages varied from 20 to 38 years, with an average age of 34. Their previous civilian occupations and places of residence in the United States were inquired into, and neither was found to be a factor in the present study.

Previous medical history. A check of their previous medical history revealed nothing in any of these patients that was a factor in their present complaints. There were 6 old injuries to lower extremities, but none of these was considered a factor in the present complaints.

Experience at the time of sinking. A study was made of the experiences at the time of the immersion, in order to determine the various factors which might throw some light on the present complaints. Inquiry was made as to the question of injury at the time of sinking, and 9 were found to have received minor injuries at that time, none of which injuries were considered to be factors in their present complaints.

All 65 men had their legs more or less in the water following the sinking; either in the sea, or in lifeboats partially filled with water, or in rafts partially filled with water.

The legs were in the water in this manner from 1 to 10 hours, with an average time of 5½ hours. The water temperature varied from 28 to 38 degrees, evidently depending on whether or not the men were in the vicinity of the Gulf Stream.

An attempt was made to determine how these men were clothed, particularly with reference to their lower extremities, in order to see how such clothing might affect their original condition and follow-up results. The largest group was wearing government issue clothes, with ordinary government issue shoes and light woolen socks. There were 26 in this group; 24 of them had complaints, and 19 showed abnormal physical findings. In the next group, made up of Air Force enlisted men, high leather boots and heavy woolen socks were worn. There were 7 of these men; all 7 had complaints, and 4 showed abnormal physical findings. In another group, made up of 5 men, light wool socks only were worn; all had abnormal complaints and physical findings. In another group of 5 men, government issue shoes only were worn, and all had complaints and abnormal physical findings. The 2 men remaining did not recall what clothing they had on their lower extremities while in the water; both had complaints and abnormal physical findings.

No deduction can be made as to the benefit any particular type of clothing for the lower extremities would afford under the circumstances as they existed.

Of 51 men checked, the effect of the cold immersion was so marked that, in getting aboard the Coast Guard boats picking up survivors, 38 of them needed assistance and were hauled up on the boats by ropes. Only 13 were able to get into the rescuing boats unaided, and it is notable that of these 13, 8 were in a lifeboat with water only up to their knees, for a period of 3½ hours. The rest of the men who did not need assistance were either in the sea or practically submerged on rafts for a period of 4 to 5 hours. Of this group who did not require assistance in getting aboard the rescuing boats, 9 had symptoms at the time of examination and 7 had abnormal physical findings. All the men who needed assistance in getting on board the rescuing boats complained mainly of numbness or lack of co-ordination in their legs, so that they had difficulty in walking; and the treatment on the boats consisted in the removal of wet clothes, rub downs, hot drinks, and general warmth.

Of the total group examined 12 were admitted to the hospital for treatment after their arrival. They had immersion foot of varying degrees, and the length of treatment varied from 1 to 17 days, with an average stay of 6½ days.

Subsequent treatment. During the 14 months since the original onset, only 1 man of the whole group was admitted to the hospital for symptoms referable to the secondary effects of immersion foot.

Eleven men came to sick call, of this group, at varying periods during the 14 months; the average number of visits to sick call being 1 to 5, and the main complaint being pains in the legs, usually treated by physiotherapy.

Present symptoms. At the present time, the following are the complaints presented by the group still under treatment:

Burning sensation or burning pain in the feet or legs while walking. Twenty-two men complained of this in varying degrees. A large number of the group had the symptoms in mild form, and thought nothing much about it until the complaint was elicited by question. In a very few it was a marked complaint.

Numbness of the legs. This was one of the main complaints, and existed in 27 of the group examined. It was of varying degree, mainly existing at rest and particularly at night in bed in conjunction with rest pain.

Intermittent claudication. True intermittent claudication to the extent that the patient needed to stop and rest after walking a short distance, due to calf cramps, existed in only 8, and was quite severe in degree. Of the form of intermittent claudication known as *forme fruste*, characterized by weakness of the leg muscles on walking a short distance and requiring stopping to rest before going on, there were found 25 complaints. Of the form of intermittent claudication characterized by pain in the buttocks and legs simulating sciatica, there were 4.

Rest pain. This was found as the most common and severe complaint of the group examined. It was found in 30 of the group, and was characterized mainly either by cramp-like muscle pains or general aching of the lower extremities occurring at night while patient was in bed and associated with numb-

ness and subjective coldness of the legs and feet. It is to be noted that this symptom was the one most bitterly complained about by the men, particularly because it caused the victim to wake up from sleep during the night due to the pain, with resultant loss of rest and sleep.

Subjective coldness of the legs or feet or both. This complaint was made by 31 of the group, either referable to one or both legs or feet, and associated as here noted with rest pain and numbness. This group also complained of this symptom on going outdoors in cold weather, even when their feet and legs were warmly clothed, so that their ability to work outdoors was decreased.

Changes in perspiration of the extremities were the complaint of 26. They noted markedly increased perspiration of the feet since the initial immersion, and most of them stated that it was one of the most uncomfortable symptoms among the various complaints noted.

Changes in color of the extremities were noted by 8. The complaint usually was that the toes looked bluish-red most of the time; and 1 man complained that both feet were continually dead pale and white.

Changes in toenails were noted in 12. The changes consisted mainly of extreme brittleness or irregular growth of the nails, mainly in the big toes.

Changes in the skin of the extremities were noted in 12 of the group. The complaint was either of extreme maceration and soreness of the toes due to excessive perspiration or, and this was the main complaint, of marked dryness, scaling, and thinning out of the skin on the legs.

Objective findings. General physical findings: 8 had complaints of various nature due to their various conditions, but none of the complaints was related to, or a factor in, the complaints or findings of the extremities.

Physical examination of the extremities revealed the following: no muscular atrophy in any of the cases examined; no bone atrophy in the few patients whose extremities had been x-rayed for other conditions. A complete x-ray study of the lower extremities of all these individuals was not made. Trophic changes were noted as follows: Changes in the hair growth of the lower extremities was noted in 6 of the individuals, consisting usually of the loss of hair on the lower extremities, markedly on the legs. In a couple of individuals this was patchy, but usually it involved a complete hair loss on the legs from the knees down. Changes in the nails were noted in 14 patients. The change usually consisted of brittleness, extreme thickness, and deformed growth of the nail. It was usually found in one or two nails, and quite commonly in either the big toe or 5th toe on one side or the other, usually associated with pain in the toe; and usually associated with a history that the particular toe had been the one most involved at the time of the original immersion. Changes in skin were noted in 7 patients. This consisted of a dryness, thinning out, and scaling on the legs, usually patchy. In those patients complaining of excessive perspiration, some maceration was found between the toes, and occasional evidence of epidermophytosis went along with it. It is further noted that in those patients originally admitted to the hospital with ecchymotic areas, or blebs, or with superficial gangrenous areas, the resultant scar formation in the skin was extremely pale and atrophied in appearance.

Color changes were noted as follows: Ischemia was tested for by elevating the feet 45 degrees plus motion of the leg muscles by repeated extension and flexion of the foot. Plantar ischemia was noted in 17 cases. This was usually found unilateral, was varied in degree, and was usually found on the side corresponding to the region complained of mostly by the patient. Dependent rubor was found in 34 of the patients examined. How much value this physical sign has in the presence of peripheral vascular disease of this type is hard to determine. The fact that it was found so commonly among these patients with complaints may be of some significance. Cyanosis was found in 3 patients with complaints, and in each case consisted of cyanosis confined mainly to the big toe, in patients whose toe was morbidly involved at the time of the immersion. Varicose vein formation was found in 11 patients, developing at various times during the 14 month period. This

condition was usually confined to one leg, which leg was the one usually most involved at the time of the original accident. The varicosities were usually mainly small, superficial, and confined to the foot or lower leg. There was no evidence found of superficial migratory phlebitis, such as one finds in thromboangiitis obliterans. One patient presented evidence of a deep phlebitis with some edema of the ankle; otherwise, no edema was noted.

Examination by palpation revealed in 9 cases a definite difference in surface temperature to hand touch. This consisted of marked coldness of one extremity as compared with the other; and the cold extremity usually corresponded with the region of most complaint of the patient. No facilities were available for skin thermocouple studies. No changes in the peripheral arteries were noted except in pulsation of the dorsalis pedis artery. In 13 of the cases the pulsation of this artery was markedly decreased. This was almost always a unilateral finding, corresponding to the extremity most complained of by the patient. There were no changes referable to consistency, thickness, or tenderness of the peripheral vessels. Arteriography was not done in the study of these cases. No facilities were available for detailed capillary study. Histamine reactions were done in 1 case, the most severe of the group, and the flares in the left leg were noticeably decreased, corresponding mainly to the most involved area.

Abnormal neurological findings were obtained in 3 cases: One man showed loss of sensation of the outer left foot, corresponding with the area in which he complained mainly of burning pain when walking. A second man was found to have spotty anesthesia of both legs, combined with hair loss in the corresponding area. A third man was found to have hyperesthesia of both outer lower legs, corresponding to his pain reference areas. No other abnormal neurological findings were obtained.

Various other abnormal physical findings in the extremities were asymptomatic pes planus, epidermophytosis, and in 1 case an extensive scar with slight deformity of the tibia due to an old compound fracture. In all cases it was considered that these findings were not contributory to either the complaints or physical findings referable to the patients' extremities.

SUMMARY AND CONCLUSIONS

A group of 65 patients were studied 14 months after the incurrence of immersion foot. Of these, 49 had been found to have complaints, and 42 had been found to have abnormal physical findings associated with chronic peripheral vascular disease, secondary to immersion foot.

1. Secondary symptoms and findings following immersion foot are quite common and more persistent than usually thought.

2. The main complaints are evidently rest pain, numbness of the legs or feet, subjective coldness of the legs or feet, and increased perspiration of the extremities.

3. The incidence of abnormal physical findings, particularly plantar ischemia, development of superficial variocosities, and decreased peripheral arterial pulsation of the dorsalis pedis artery, mainly unilateral and corresponding to the primarily affected extremity, exists in a surprisingly high proportion of patients presenting complaints.

4. It is our opinion that these complaints and findings are on the basis of fibrosis of the extremity, secondary to the initial inflammatory reaction after immersion, rather than to secondary angiospasm.

5. The persistence of peripheral vascular disease, secondary to immersion foot, should be brought to the more serious attention of surgeons dealing with immersion foot. This is particularly true in view of the fact that these cases may be a source of future persistent disability and liability to the government.

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TERATOMA OF THE OVARY

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TERATOMA of the ovary, otherwise known as teratoblastoma, embryoma, or "solid" dermoid, has been of surpassing interest to pathologists since early days. This has been true not merely because of its rarity and because its derivation has remained obscure, but, particularly, because a more complete understanding of these remarkable tumors may be the key which will serve to explain the nature of other rare ovarian growths.

Although encountered in other organs and tissues of the body, teratoma is predominantly an ovarian tumor and it is here that it is found in most developed and characteristic form. It is usually a compact, solid, rapidly growing neoplasm composed of tissues which are frequently wholly undifferentiated, corresponding to various stages of fetal development and revealing only isolated tendency to more completely developed organ-like formation. The material entering into the structure of dermoids and teratoma is the same, all three germinal layers represented in both; the differences lie apparently in the tissue of origin and in the fact that dermoids are comprised of mature tissues whereas a teratoma consists of embryonal elements. The great characteristic of teratoma is the loss of proportion in its structure. There is topographical confusion.

Opinions differ in judgment of the malignancy of teratoma; it is a growth characterized by capacity for great proliferation, not ascribable to carcinomatous or sarcomatous degeneration but an inherent property of the cells which constitute it. Therefore, it is to be regarded as potentially malignant in all cases, unquestionably malignant in most instances.

The tumor is usually nodular or lobulated, often with projecting cysts, of astonishingly large size for so malignant a neoplasm (due to rapid growth?), often the size of a man's head. It may be spherical, ovoid or of ovarian shape, is usually pedunculated, as in our case, of varied color—gray, yellow, red, blue, brown. The consistency is usually soft, but many are firm. This feature varies not only with various tumors but also in the same growth, e.g., marrow-soft to firmly elastic. A capsule is usually present but may not be clearly defined. Perforation of the capsule is frequent, but by no means usual. The cut surface reveals a multitude of variations. It is polymorphous, polychromic. Cystic spaces are of varied form and size; the contents may be clear, slimy, colloid, fatty, honeycombed, or spongy. There may be gray, straw-yellow, pinheaded black points, or homogeneous or hemorrhagic red-brown tissue in solid, lamellated, brain-like or marrow-like masses. Strands of dense fibrous tissue are usual. Areas ranging from larger portions or organs or viscera (rare) to minute microscopic rudiments may be found.

Microscopically, the picture is that of chaos. The tissues are mostly fetal in character, but not entirely and invariably so. It is characteristic for well differentiated tissues to lie immediately adjacent to lawless and wild areas of potentially or definitely malignant epithelial, endothelial, or sarcomatous pattern.

One element of a teratoma may suppress growth of the others. Such one-sided development is unusual, yet it presents the very important question as to how far apparently simple tumors of the ovary may be of teratomatous origin.

It is difficult to gauge the number of these growths which have been discussed in the literature since the days of Virchow, perhaps 200 to 300, all told. In Kermauner's clinic in Vienna, among 1300 ovarian tumors throughout a period of 30 years only 2 were teratoma. Intermediate or transition forms between dermoid cysts and teratoma occur rarely, if ever; probably there are some.

Metastases occur most often in the abdomen but may appear in distant parts of the body. They present either a counterpart of the original tumor or a more simple structure, i.e., a purely sarcomatous or carcinomatous growth,

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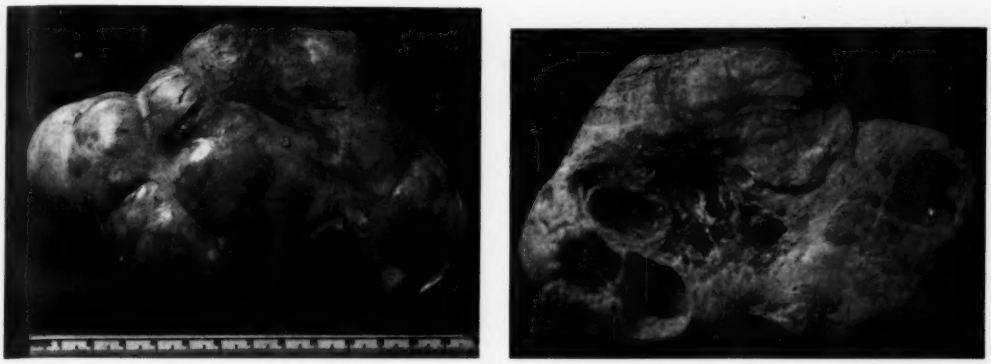

Fig. 1. Teratoma of ovary.

a glial tumor, a chorioepithelioma, or a malignant tumor of undifferentiated cells.

Teratoma is a tumor of childhood and early maturity, mostly before the age of 35. Not more than 5 recorded cases have been found after the menopause.

The etiology of teratoma remains unsolved. The growth must be derived from a cell that can produce all three embryonic layers; as expressed by Askanazy, the origin must be from a toti-potential cell. Only two theories of origin are prevalent, that isolated blastomeres (Marchand-Bonnet theory) are the source of these trigerminal growths or that they arise from primitive unfertilized ova.

Our tumor was removed from a woman of 63, the mother of 4 healthy children. Her father and one brother died of carcinoma. Three years earlier there had been some genital bleeding and vaginal removal of a fibroid tumor and polyps; no malignancy was found. At the time of our examination the patient complained of vaginal burning without discharge and a tumorous enlargement of the abdomen. There were no symptoms or evidences of endocrine abnormality.

At operation, February 6, 1945, the liver was firmly and inseparably adherent to the anterior abdominal wall, the pancreas was indurated, the upper abdomen otherwise negative. There were some adhesions about the cecum. The left ovary was converted into a freely movable, pedunculated, irregularly nodular massive tumor with a smoothly lobulated external surface. The right ovary was atrophic. The generous-sized uterus contained one small interstitial myoma and one bean-sized sessile polyp; the endometrium was rather thick for an elderly woman.

The irregularly nodular, smoothly lobulated, 14 by 9 by 6 centimeter tumor represented the left ovary (Fig. 1). The outline was roughly triangular in shape, one surface strand demarcating the mass into a major, giant kidney-sized and a minor, asymmetrical, orange-sized smaller lobe. Some of the lobules projected from the surface as firm nodules up to 4 centimeters in diameter. The entire surface was firm except over one-tenth of its area, which was cystic. The color of the fresh specimen varied from bluish to reddish gray.

On bisection, the surface presented a solid, apparently malignant tumor with numerous cystic cavities up to 3 centimeters in diameter, variously filled with clear, turbid, slimy, colloid or hemorrhagic fluid, and a varied amount of necrotic débris. Some of the solid cut surface was fibrotic and firm but the major portion was of the consistency of a parenchymatous organ such as the liver or kidney, the color greatly varied from pink to gray-brown, a kidney-brown color predominant. Many pinhead to pinpoint black spots were visible. Trabeculations of the stroma were clearly evident.

The microscopic picture verifies Askanazy's emphasis that often the constituents cannot be distinguished, as was evidenced by the long, confusing discussion of the distinguished pathologists during the conference at which he

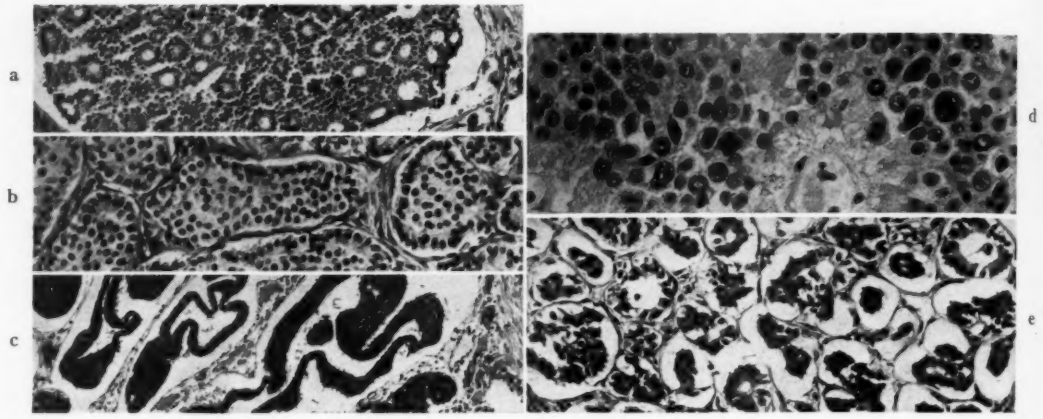

Fig. 2. Photomicrographs of sections from various regions of the teratoma.

presided. No portions of organs, such as are sometimes illustrated, are present in our specimen, thus evidencing the embryonal nature of this growth. It is a true blastoma. A variety of cellular structure is evident in amazing detail and with great clarity, in contrast with all illustrations which have been available to me in the literature. Organoid forms are suggested but surely not to be undeniably identified as such. In Figure 2 a are tubules resembling glands along the intestinal tract. Figure 2 c presents epithelial configurations of medullary tube-like structures. Figure 2 e reveals a mesonephroid type of tubules, not unlike those of arrhenoblastoma. Massive islands of epithelial cells, such as in Figure 2 b, but often of much greater size, dominate the field in the majority of microscopic sections. Masses of immature cells, such as those in Figure 2 d, and extensive wildly growing sarcoma-like and carcinoma-like areas in abundance appear under the microscope adjacent to well differentiated islands of cells such as those of Figure 2 b.

The more one studies the polymorphous microscopic picture presented by this tumor, the greater the temptation to join the ranks of those who ascribe a teratomatous origin to many rare kinds of tumors of the ovary. This statement does not gainsay the evident origin of Brenner tumor and some pseudomucinous cystadenomata from the peritoneal epithelium of the uterine adnexa.

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ONE STAGE "OPEN" RESECTION OF LESIONS OF THE LEFT COLON WITHOUT COMPLEMENTARY COLOSTOMY

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COLON resection has gone through a process of evolution that will prove to be nothing short of remarkable for the half century in which it has been performed. The earliest procedures consisted of primary anatomosis of the open colon with such disastrous mortality from peritonitis that the contribution of Mikulicz (12, 13) in 1903 was widely accepted as the procedure of choice when he reported a 16.6 per cent mortality for 24 patients operated upon by the principle of exteriorization. Mikulicz was not the originator of this plan of resection, but his relatively large series of cases was so convincing that the procedure has been identified with his name. The Rankin obstructive resection (1930) was an improvement, but even at that time Rankin recognized the desirability of a primary resection, but deterred because he did not think it could be done safely.

The next phase in this development was the performance of one stage ileocolostomies with resection of lesions of the right half of the colon. A few surgeons doubted the safety of this plan as evidenced by Allen's recommendation of a transverse ileocolostomy preceding resection of the right colon (1, 2), the use by Whipple (20, 21) of the Miller-Abbott tube as complementary decompression, and the isolated position of Lahey in insisting upon exteriorization procedures for ileocolostomies. By and large this procedure as a one stage operation has been so successful in the hands of so many surgeons that little argument can now be raised as to its safety.

The next development consisted of primary resection and anastomosis of a colonic lesion with a *complementary* appendicostomy, cecostomy (10) or colostomy, as recommended by Wilkie, Allen (1), Whipple (20), Cheever, Dixon (6), Stone and McLanahan, and White. In the hands of those insisting upon this auxiliary vent, the mortality rate decreased one-half or more when this feature was added. Dixon (5) must be credited with the extension of this procedure to lesions of the pelvic colon, but always concluded his operation with a transverse colostomy which was closed 3 to 6 weeks later.

The most recent development has been in the execution of a one stage resection and anastomosis without the proximal vent. Cheever, and Stone and McLanahan were discouraged by the higher mortality rate attendant upon this method, but Campbell did not find that the creation of the external vent was essential. In what perhaps represents the most thorough presentation of this subject to date, Wangensteen (19) reported favorably upon 61 patients operated upon by this plan with an overall mortality of 1.6 per cent, although 1 patient was given a proximal appendicostomy, 2 had cecostomies, and 6 came to operation with previous colostomies performed for release of obstruction. Wangensteen, however, makes an issue of the importance of a "closed" method of anastomosis using a clamp technique and theoretically attaining asepsis.

We should like to give a preliminary report of our first 20 operations, from the private surgical service of one of us (K.A.M.), performed during the past 2 years, using an "open" method of anastomosis. Though the period of observation is short and the series of cases limited, we believe that the trend has been clearly indicated. We were encouraged to attempt this plan of treatment by the availability of such modern adjuncts to bowel surgery as succinylsulfathiazole, multiple blood transfusions, fluid and electrolyte balance, parenteral sulfonamides, spinal anesthesia, oxygen inhalation, intestinal decom-

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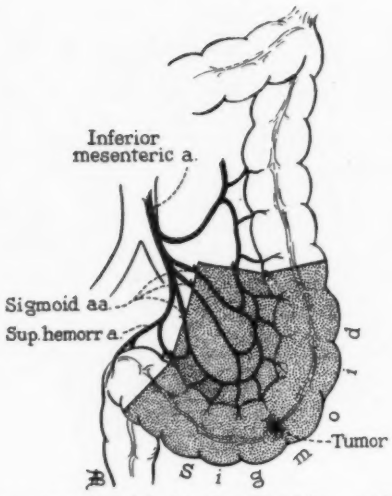

Fig. 1. Drawing of the blood supply of the rectosigmoid to illustrate the points of ligation of the blood supply to permit as much collateral circulation as possible. The shaded area is the portion of colon to be resected and a wedge shaped portion of mesentery to be removed with it.

pression, and the use of the interrupted permanent sutures. We have thus witnessed a phenomenon in which the cycle of development returns to its very start, but the improvments which have occurred in the interim have turned an earlier failure into a success.

CLINICAL DATA

Age and sex. The 20 cases were evenly divided as to sex and the range was from 39 to 72 years, with an average of 64 years. Age or sex did not influence our preoperative or postoperative management, although the only 2 instances in which we used an inhalant anesthetic were 2 nervous females who insisted upon being unconscious. The occurrence of atelectasis, embolism, and edema was seen postoperatively only in patients past 70 years of age of whom there were 4. Metastases of the primary lesion were seen more frequently in the younger patients.

Diagnosis. The diagnosis was usually made by a history of bleeding or change in bowel habit and the identification of a mass by palpation, proctoscopic examination, or barium enema. Two of our patients were operated on with a preoperative diagnosis of pyloric obstruction, and succinylsulfathiazole therapy was omitted. None of our patients in this group presented the picture of colon obstruction for obviously they were not candidates for the type of surgery contemplated here. The proctoscopic examination became even more important here for the recognition of the distance between the pectinate line of the rectum, and the lower limit of the lesion is of importance in the decision as to whether the patient will be best treated by an abdominoperineal resection or a procedure which will preserve the rectal sphincter. Wangensteen (19) has shown that lesions 13 centimeters above the pectinate line are resected and anastomosed with much greater ease, but does not hesitate to do an ampullary resection for a lesion within 10 centimeters of the pectinate line. Dixon (5), on the other hand, has not reported resections below the level of the rectosigmoid.

Succinylsulfathiazole. This drug was administered to all but 2 patients for a period of 7 to 14 days before surgery in doses varying from 12 to 18 grams per day. The usual routine for administration of the drug was for the patient to take the drug at home in the prescribed dose after catharsis, cleansing, and low residue diet, and to continue until entrance to the hospital. At this time an enema and castor oil (1 ounce) were repeated and the drug continued until the time of the operation. No further enemas were administered, especially during the 24 hours immediately preceding operation. When the latter precaution is not taken, an occasional patient will show enema fluid proximal to the lesion which can be a source of peritoneal soilage in an open anastomosis. Instead of beginning with the 24 hour dose as the initial dose, we preferred to build up more gradually with the thought of thereby avoiding gastrointestinal complaints which often develop in patients receiving this drug. No patient received less than a total of 84 grams of the drug, the highest total being 216 grams. The drug was usually not resumed after operation because of the routine use of an inlying intragastric suction tube. However, the patients did receive sulfanilamide intraperitoneally and sodium sulfadiazine intravenously on the first and second postopera-

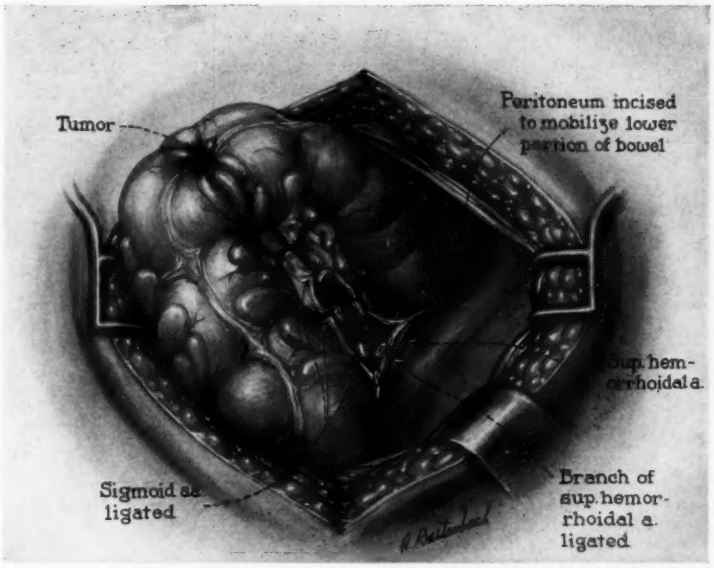
Tumor
Peritoneum incised to mobilize lower portion of bowel
Sup. hemorrhoidal a.
Sigmoid a. ligated
Branch of sup. hemorrhoidal a. ligated

Fig. 2. Artist's drawing illustrating the mobilization of the sigmoid colon by division of the parietal peritoneal reflection and ligation of the sigmoidal branches of the inferior mesenteric artery and of maintaining the superior hemorrhoidal artery.

tive days. The 2 patients who inadvertently did not receive succinylsulfathiazole were those with incorrect diagnoses; resections were performed successfully in both of these without complications.

Blood transfusions. The average amount of blood transfused in this group of patients was 1,350 cubic centimeters and varied from 500 to 3,500 cubic centimeters. Since we were dealing with private patients, the need for massive transfusions was probably not as great as we have seen in patients from our charity wards who enter the hospital in a later stage of the disease, are more apt to show anemia, and present a more profound nutritional problem. When more than one transfusion was necessary, we preferred to give it one or more days preoperatively so that its effects would become more manifest. Although no amino acids were used in this group of patients, we have already reported its use in other cases and are well aware of its potentialities (11).

Operative procedure. In 18 of the 20 patients spinal anesthesia was used; in 2 of the 18 pontocaine was used, in the remainder a 1:1500 solution of nupercaine with the technique of Hand and Sise. In 2 patients in which an inhalant was deemed advisable, combinations of ether and ethylene, and ether with cyclopropane were used. Our only death was in the patient receiving ether and ethylene.

The duration of the operation varied from 1 hour and 10 minutes to 2 hours and 40 minutes, with an average of 1 hour and 45 minutes.

The details of the operative technique are shown in Figures 1 to 4. It should be mentioned that no crushing clamps were used, interrupted catgut sutures were used through all layers, and interrupted No. 35 stainless steel wire sutures were placed as a second seromuscular layer. The latter were used as Lembert sutures. Sulfanilamide crystals in quantities up to 5 grams were sprinkled between the first and second rows of sutures and about the anastomosis itself. At the conclusion of the operation the rectal sphincter was dilated and a rectal tube was inserted to a point below the level of resection.

Pathology. The size of the lesions varied from involvement of a 1.5 centimeter segment

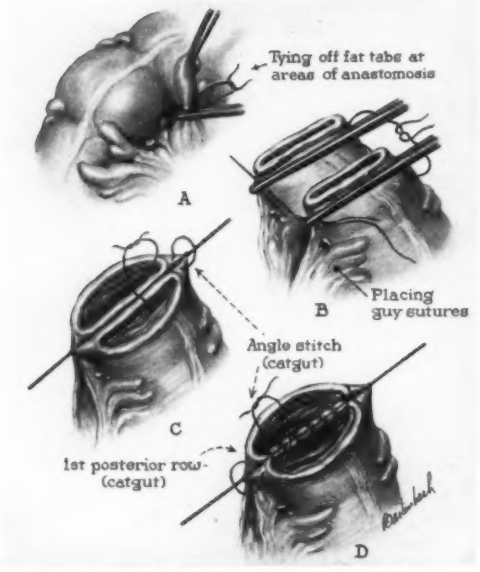

Fig. 3. A, The colon is prepared for anastomosis by freeing the epiploic fat tabs and ligating them so as not to deprive the bowel of the blood supply they contribute. The bowel is then resected between straight intestinal clamps and left on only until, B, two guy sutures are placed in the serosa to hold the distal and proximal loops together. In C, the placement of "angle stitches" is demonstrated in which the suture is introduced from the mucosal surface of one loop, brought out through the serosa of the opposite loop, and emerged at the mucosal surface of that loop; the knot therefore lies on the inside of the bowel lumen. D, The placement of a series of interrupted catgut sutures incorporating all layers in the first posterior row.

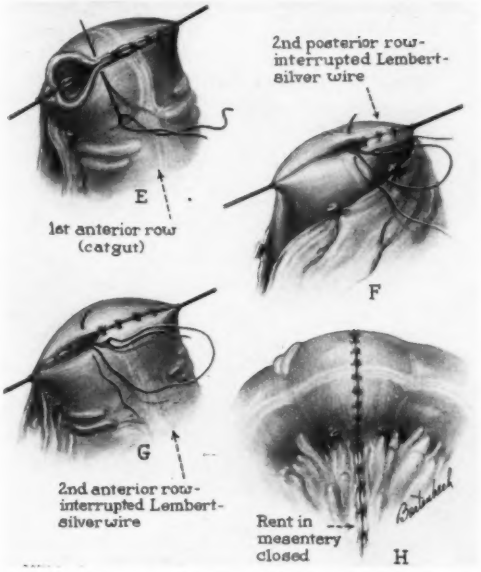

Fig. 4. E, The continuation of the first row of sutures on the anterior surface consisting of interrupted catgut sutures through all layers as in Figure 3, D. The inversion of the mucosal edge is accomplished with the next row of sutures. F, The placement of the second row of sutures consisting of interrupted Lembert stitches of No. 35 steel wire on the posterior surface of the anastomosis and also on the anterior surface. G, The defect in the mesentery is closed with interrupted catgut. The bowel is then returned to the abdominal cavity and the wound is closed in layers. The fact should be emphasized that no complementary colostomy has been employed in the series of cases which are herein reported.

of bowel wall to a 14 centimeter segment. The sigmoid colon was the site of the lesion in 11 cases, the transverse colon and splenic flexure in 1 case each, the descending colon in 4, and the rectum in 3. The lowest lying lesion in the series was 5 to 6 centimeters up from the anorectal juncture, and the lesion histologically proved to be a lipoma. Eighteen of the lesions were adenocarcinomas, either papillary, mucoid, or annular in type. One case was that of a stercorous ulcer due to an impacted fecalith, and the remaining one was the aforementioned lipoma. In 5 patients, the regional mesenteric lymph nodes contained metastases, while in another 3 cases the enlarged nodes proved to be inflammatory in nature. Omental nodes were present in 1 patient, liver metastases in another, and ovary metastases in another.

Postoperative course. All patients were placed after operation on continuous siphonage, parenteral fluids were administered in quantities necessary to maintain fluid balance and a good urine output, and hyperventilation was obtained with mixtures of oxygen and carbon dioxide. Although peak rectal temperatures to 104 degrees Fahrenheit were seen occasionally, these were the exceptions. In most patients a remarkably afebrile course was characteristic after the second or third postoperative day. Gastric suction was discontinued as soon as the patient first passed flatus, which was usually on the 3rd or 4th postoperative day. Oral feeding was usually started on the same day. In 6 patients the first formed stool was passed on the 3d postoperative day, in 1 on the 4th, in 5 on the 5th,

in another 5 on the 6th, in 2 on the 7th, and in the remaining patient on the 10th postoperative day. This early return of bowel function was unassociated with diarrhea or bleeding, except in 1 patient who later proved to have a nonspecific ulcerative colitis. When there was a delay in bowel function without evidence of organic obstruction, patients were given prostigmine in repeated doses.

The period of postoperative hospital stay averaged 13 days and ordinarily ranged between 10 and 15 days. The patient who had the ulcerative colitis remained in the hospital 49 days.

Complications. Pulmonary atelectasis occurred in 2 patients, pulmonary edema in 1, and pulmonary embolism in 1; all of these patients were 70 years of age or older. A wound infection which required readmission for drainage occurred in 1 patient. An urethritis in 1 patient followed repeated catheterization. In 1 a nonspecific ulcerative colitis became apparent during the postoperative course. There was 1 death (the case of embolism) which occurred on the third postoperative day, giving a mortality of 5 per cent.[1]

DISCUSSION

Orthodox teaching had heretofore condemned any attempt to resect, anastomose, and return the colon to the peritoneal cavity on the following grounds:

1. The blood supply of the colon is too poor to depend upon satisfactory healing; i.e., a leak at the anastomosis is far more imminent than in an anatomosis higher in the gastrointestinal tract.

2. The high bacterial flora of the colon could not be adequately controlled by enemas alone, and peritonitis and wound infection were considered inevitable sequelae.

3. Postoperative distention would jeopardize healing at the suture line by increasing intraluminal tension.

With the advent of modern preoperative and postoperative care, this concept requires re-evaluation.

Better anatomical appreciation of the blood supply of the colon has taught us that a primary anastomosis can be done if we stay within the boundary of the marginal branches of the left colonic, sigmoidal, and superior hemorrhoidal arteries, as the case requires; i.e., if care is shown in the ligation of vessels so that only the branches to be resected with the specimen are ligated and the mesentery is left intact to within a centimeter of the line of resection. Dixon (5) has pointed out that the middle and inferior hemorrhoidal arteries supply the pelvic colon so freely that branches of the superior hemorrhoidal arteries or even the terminal branches of the sigmoidal arteries can be ligated without fear of necrosis of an anastomosis of the colon beneath the brim of the true pelvis. He has also pointed out that a freer anastomosis occurs between the superior, middle, and inferior hemorrhoidal arteries than is commonly appreciated. Singleton, in pointing out several anatomical principles in surgery of the colon, has emphasized freeing a minimum amount of mesentery, removing more of the antimesenteric border of the bowel than of the mesenteric side, and utilizing the appendices epiploicae when possible. When it is necessary to remove the epiploic fat, Singleton cautions one not to ligate the artery entering the bowel at that point.

Many of us have gone through more than one era of new instruments and one wonders whether a crushing instrument does not have less place in primary surgery of the colon than elsewhere in the gastrointestinal tract. Whatever advantage may be gained by the so called "aseptic anastomosis" or "closed" technique is paid for at the price of crushed bowel edges, which the colon will tolerate much more poorly than will the stomach or small bowel. We feel that peritonitis due to soiling at the time of anastomosis is no longer a major threat to bowel surgery with the protection afforded by the sulfonamides and still newer chemotherapeutic drugs which promise to attack even the gram negative bacilli. As Coller has pointed out, the more serious form of peritonitis occurs from a continuous leak of intestinal content through a faulty anastomosis and not from soilage at the time of resection. Our attitude is that a crushing clamp predisposes to necrosis which may slough many days later.

[1]Since preparation of this manuscript the authors have successfully operated upon 5 more patients, reducing the mortality rate to 3.8%.

The single most important contribution that encouraged us in this plan of therapy is the availability of succinylsulfathiazole, even though we went ahead with a primary resection in 2 patients who inadvertently did not receive any of the drug preoperatively. Not only does this drug effectively reduce the coliform count of the stool (14) but its effect upon stool size and consistency is a favorable one. The combination of succinylsulfathiazole in the colon and sulfanilamide in the peritoneum was unassociated with a single instance of peritonitis, and only one of wound infection. This would appear to be significant. Some improvement in the clinical administration of the drug is possible such as giving the patient a 3 gram tablet instead of the 0.5 gram tablet. Sulfathalidine (phthalylsulfathiazole), which is believed to be just as effective as succinylsulfathiazole, requires one-half the dose of the latter and offers some advantage. We have dispensed with the initial administration of the 24 hour dosage and feel that the slower attainment of the desired level is less apt to produce diarrhea. Instead of calculating the dose on the basis of ¼ gram per kilogram of body weight, we have arbitrarily ordered the drug in doses of 12, 15, and 18 grams per day depending upon the body weight. In the majority of the cases we did not resume succinylsulfathiazole postoperatively for all of our patients were routinely treated with Levine tube gastric suction siphonage after operation. Sodium sulfadiazine was given intravenously in 5 gram doses on the first and second postoperative days as a routine.

The importance of blood transfusions cannot be overemphasized. In addition to restoring or increasing the circulating volume, correcting an anemia that might be masked by dehydration, elevating the circulating plasma proteins, preventing shock, sparing tissue protein for use elsewhere, and contributing many factors concerned in the body's resistance to infection, it offers one more as yet unexplored possibility. With the increased number of erythrocytes there is an increased oxygen capacity of the blood which should aid in maintaining the viability of a tissue, the blood supply of which is limited. Adequate blood transfusions, by increasing the protein content of the body, favorably affect wound healing, gastrointestinal motility, edema of the anastomotic stoma, and obviate pulmonary complications. Time is necessary for the achievement of all these benefits and therefore transfusions should be given over a period of several days prior to operation. The infrequent occurrence of shock and its transitory nature (when it does occur) is striking in those patients given sufficient blood prior to surgery.

Unless there is obstruction prior to operation, in which event the patient is certainly not a candidate for primary resection, postoperative distention can be prevented with a well functioning intragastric tube. We have learned from Wangensteen (18) that 80 per cent or more of intestinal gas is swallowed atmospheric air, and evacuation of this air before it can enter the small and large bowel becomes an effective therapeutic plan. Although the passage of a Miller-Abbott tube might offer theoretical advantages in having the decompression closer to the site of anastomosis, and in utilizing the remainder of the gastrointestinal tract proximal to the suction holes for absorption of fluids and calories, the passage of this tube requires considerable effort and technical skill, so that it is usually reserved for the obstructed patient. Furthermore, experience has shown us that ileocecal sphincter not infrequently resists entrance of the balloon of the Miller-Abbott tube and its actual progression to the left half of the colon is arrested. The passage of the Levine tube, which we prefer, should be carried out before operation so that the aspiration of any swallowed inhalant anesthetics, if a general anesthetic is required, will eliminate another cause of postoperative distention. Such a tube may prevent an aspiration pneumonia, which can follow any anesthetic. The practice of preventing increased intracolonic pressures by passing a rectal tube proximal to the anastomosis (19) is not carried out without trauma and should be done with caution. We have aided decompression by dilating the rectal sphincter by digital means and inserting a rectal tube, but not to the level of the suture line.

The use of interrupted sutures has an understandable advantage. With the use of such sutures too much faith is not placed upon a

single strand and the circumference of the lumen is not encroached upon. Use of fine stainless steel wire as an interrupted seromuscular suture avoids the capillary attraction of exudate through strands of catgut or silk, and therefore is less apt to create a sinus through which infection might drain. A permanent suture is a safeguard against a delayed separation when catgut begins to weaken and dissolve. The use of a Lembert suture has given us very satisfactory inversion without creation of a diaphragm which is more apt to follow the use of a thick row of several sutures. Similarly, the use of interrupted steel wire in the closure of the wound (8) not only lowers the incidence of wound infection, but permits these patients to get out of bed earlier and thus tends to avoid the pulmonary complications that go along with prolonged bed rest. The closure of the resected mesentery with fine sutures, which avoid inclusion of important blood vessels, is still another important detail.

Our preference for spinal anesthesia is based upon excellent relaxation, a quiescent gastrointestinal tract, and reduced likelihood for emesis or tracheal aspiration after operation. The duration of anesthesia provided by nupercaine (7) 1:1500, or pontocaine has always been adequate. We have given general anesthetics only on the insistence of the patient.

Thus far we have discussed only why primary resection and anastomosis of the left half of the colon could be performed as safely without a proximal vent or safety valve as with it; we have said nothing of its *advantages*, of which there are many. First and foremost, a more radical resection is possible for more dissection can be done for the purpose of removal, and less for the purpose of developing a proximal and distal loop for the exteriorized segment. Implants at the site of a former obstructive resection have not been unusual and one wonders if this recurrence could not have been avoided if the segment had been resected instead of placed as a septal spur.

Second, exteriorization operations show a high incidence of complications, among which are retraction of either or both loops, wound infection, herniation, prolapse, fecal fistula, obstruction, and stricture formation. All of these add to an overall mortality and morbidity.

Third, a temporary colostomy should be avoided if there is an alternate procedure that guarantees as low a mortality and as successful a result. Our mortality of 5 per cent is acceptably low, especially since pulmonary embolism takes its toll in spite of our best preventive efforts. If the mortality of subsequent closure of a colostomy is added to that of the initial procedure, the comparison will favor the procedure we have recommended.

The fourth point is that of economy. An average 13 day postoperative course is possibly a new low for this type of procedure. Avoidance of further return visits to hospital for closure of colostomies or correction of complications has considerable practical merit.

In spite of the many advantages there are contraindications for this procedure. Obviously, a patient with a distended colon due to obstruction is not a candidate for any type of resection and only a preliminary decompression colostomy should be done. Earlier diagnosis of lesions of the left half of the colon, which are more prone to produce obstruction than in the right half of the colon and are within the reach of the proctoscope and sigmoidscope in the majority of instances, will spare more patients this complication. If the lesion has perforated and produced a fistula, abscess, or peritonitis, a one stage resection would be ill advised. Lesions which lie below the 10 centimeter level should be accurately appraised for size, fixation, and regional extension because of the increased technical difficulties of an anastomosis at this level. No compromise should be made with the principle of a radical removal of all lymph bearing tissue for our first consideration should always be eradication of the carcinoma, and our second consideration preservation of sphincter function. In obese patients with a short, fat mesentery there may be difficulty in approximation of resected loops without tension.

SUMMARY

1. A preliminary report of 20 cases of one stage resection of the left half of the colon by an "open" technique is reported in which there was a mortality of 5 per cent.

2. Requirements which must be satisfied before this procedure is undertaken include: succinylsulfathiazole, adequate blood transfusions and/or amino acid therapy, intragastric suction siphonage, oxygen inhalation, an anesthetic agent with a quieting effect upon the gastrointestinal tract, and use of fine permanent interrupted sutures in bowel and wound.

3. The advantages of the one stage resection without complementary colostomy include: (1) more radical resection of the tumor, (2) obviation of complications inherent in exteriorization procedures, (3) avoidance of a colostomy, and (4) shortened postoperative course and fewer re-admissions.

4. This procedure should not be tried in presence of a distended colon, in lesions fixed close to pectinate line of rectum, in presence of infection, and in a patient with a short mesentery.

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TRANSURETHRAL RESECTION FOR PROSTATIC HYPERTROPHIES OF LARGE SIZE

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DURING the years 1942, 1943, and 1944, operations for the relief of prostatic obstruction were performed upon 1150 patients by my associates and myself at the University of Michigan Hospital. A detailed clinical analysis has been made of this entire series of cases and is being reported elsewhere. Ninety-six per cent of the patients were operated upon by transurethral resection, while 2 per cent had perineal prostatectomy and 2 per cent were treated by suprapubic enucleation. Among the 1104 patients who had transurethral resection, 162 were found by tissue examination to have cancer of the prostate while 942, 85.4 per cent, had benign lesions, and of the latter there were 176 who had glands of large size, i.e., 50 grams or more of tissue was removed at operation, and this group of cases comprises the basis for the present report.

The youngest patient was 48 years old and the oldest was 88, while the average age of the entire group was 69.8 years. The amounts of tissue removed are particularized in Table I.

The operating time in all of these cases was less than 1 hour, save in 3 or 4 instances in which the operation was concluded in 65 to 70 minutes. It has been our belief that longer operation time subjects the patient to a disproportionate risk of shock, so we have followed the practice of limiting the operating time to 1 hour and when removal of the adenomatous mass has been manifestly inadequate, an early reoperation is carried out when the condition of the patient permits its safe performance. Secondary resection has invariably been well tolerated and none of the 5 patients who required two stage resections in this group of cases, suffered from shock or other adverse clinical manifestations at the time of secondary resection. The average amount of tissue removed was 76.4 grams. In 2 cases 160 grams of tissue was removed in one operation and in one case 190 grams was removed in a two stage resection.

Blood loss determinations were made in 154 of the cases and are listed in Table II. It is the belief of the writer that hemorrhage constitutes one of the greatest hazards of the resection operation and that immediate estimation of operative blood losses should be carried out routinely and when excessive losses are observed, transfusions of whole blood should be administered even though there are no objective signs of shock or impending shock. Forty-one of the patients were given postoperative blood transfusions. It has been our practice when operating upon patients who have very large glands, in whom great loss of blood is anticipated, to start a transfusion of blood at the beginning of operation so that the expected loss can be simultaneously replaced. Blood transfusions were administered during operation to 25 of the patients in this group.

The smallest blood loss in this group of patients is 25 cubic centimeters and the largest 1000 cubic centimeters which occurred in 2 cases. The average blood loss was 392 cubic centimeters. Postoperative hemostasis carried out by using the resectoscope was necessary in 6 cases.

A radio tube type of generator was used in all of these cases for the production of the cutting current, and a damped current generated

TABLE I.—CLINICAL DATA ON "LARGE" BENIGN HYPERTROPHY CASES—1942–43–44

Grams	Cases
50— 69	93
70— 89	41
90—119	25
120—149	12
150—and Over	5
Total cases	176
Average amount of tissue removed	76.4 grams
Largest amount—removed in 1 operation	160 grams (2 cases)
Largest amount—removed in 2 operations	190 grams

From The Department of Surgery, University of Michigan Medical School, Ann Arbor.

TABLE II.—OPERATIVE BLOOD LOSSES ON "LARGE" BENIGN HYPERTROPHY CASES

cc.	Cases
Under 100	3
100 to 199	14
200 to 349	50
350 to 499	50
500 to 749	30
750 to 900	5
1000	2
	154
	cc.
Smallest blood loss	25
Largest blood loss (2 cases)	1000
Average blood loss	392

TABLE III.—COMPARATIVE CLINICAL DATA—TRANSURETHRAL RESECTION—BENIGN LESIONS—1942–43–44

Age	Large glands (176 cases) years	All benign cases (942) years
Average	69.8	68.4
Youngest	48	15
Oldest	88	91
Hospitalization period	Days	Days
Preoperative—average	4.2	4.4
Preoperative—longest	37	66
Postoperative—average	12	11.1
Postoperative—longest	35	38
Average total hospital	16.2	15.5

by a spark gap condensor was employed for hemostasis. Whether the more highly damped cutting current that is produced by the Bovie generator would have resulted in smaller blood losses is not known. A comparative study of patients operated upon with the two types of cutting current would be of great interest.

Further data on the 176 cases having large benign glands indicate that external urethrotomy was performed for the introduction of the standard size resectoscope in 59 cases, 33.5 per cent; this constitutes a significantly more frequent need for external urethrotomy than in all of the resection cases in which urethrotomy was employed in 20 per cent. The greater need for external urethrotomy in the cases having large prostates is to be ascribed to the need for increased maneuverability of the instrument which is encountered in larger or longer prostate glands. Litholapaxy was performed in 3 cases for the removal of vesical calculi.

The period of hospitalization necessary for the treatment of prostatism constitutes one datum of interest and significance. The average preoperative hospitalization in this group of patients was 4.2 days, the longest being 37 days. The average postoperative period was 12 days with the longest postoperative period of any patient being 35 days. The average total hospitalization for the entire group of 176 cases was 16.2 days. This period of hospitalization compares very favorably with the average hospitalization for all prostates, whether large or small that are treated by transurethral prostatic resection in this hospital (15.5 days). It should be pointed out in this connection that most of the patients treated in this hospital are from out of town and of necessity are kept in the hospital longer than are those patients who live in our immediate neighborhood. We usually discharge patients on about the 10th or 12th hospital postoperative day when they live out of town, whereas patients who live in our own community are usually discharged on the 5th to 7th postoperative day.

There were 2 deaths following operation in this series of patients, thus the mortality rate for the group was 1.1 per cent. In neither of these cases was the cause of death to be attributed to the magnitude of operation performed upon the patient. One of the patients was a most unfavorable risk who had been on prolonged catheter drainage in an attempt to prepare him for some type of operation. He had, besides his severe prostatism, an organic brain syndrome and was completely unco-operative and required the constant attention of our nursing staff. Something had to be done to relieve his obstruction and continued catheter drainage was impossible. We were forced to decide between suprapubic drainage and transurethral prostatic resection, and, because of the difficulty of managing catheters of any type, we elected to perform transurethral prostatic resection. One hundred and fourteen grams of tissue was removed with a blood loss that was estimated at under 300 cubic centimeters. The patient died about 2½ weeks following operation, and it was felt that his death resulted not so much from his operation as from his debilitated condition having to do with his organic brain syndrome. The other

death occurred in a patient who was suffering from uremia on admission to the hospital and who was kept on catheter drainage for a short period of time prior to operation. Urethral catheter drainage seemed inadvisable in this case and a decision was made to perform transurethral prostatic resection rather than suprapubic drainage, in the belief that the resection operation would be no more shocking to the patient than would suprapubic cystotomy. This operation was performed early in 1942 at a time when we were performing the resection operation in spite of an elevated blood nitrogen level and unstabilized renal function. This and one other case, in the second instance a patient who had a gland of small size, both died of uremia in the early postoperative period and the cause of death was ascribed to early operation with inadequate preparation of the patient for prostatectomy. Since these two occurrences early in 1942, we have discontinued the practice of performing primary prostatic operations in the face of unstabilized, suppressed renal function, in the conviction that it is unsound practice.

In order to compare the clinical data on the group of patients having large glands with all of the benign cases treated by transurethral resection, the data have been listed in Tables III and IV. It is to be noted that in only 3 instances are there important differences in the data on the 2 groups of cases. These are the average blood losses which are significantly higher in the large gland group and are, of course, to be expected; the performance of external urethrotomy—33.5 per cent as compared to 20 per cent; and the incidence of the administration of blood transfusions, 39 per cent in the large gland group as compared to 10.8 per cent for all resection cases.

TABLE IV.—COMPARATIVE CLINICAL DATA—(OPERATIVE)—TRANSRESECTION—BENIGN CASES—1942–43–44

	"Large" glands (176 cases)		All benign cases (942)	
Blood losses (average)	392 cc.		168 cc.	
	Cases	Per cent	Cases	Per cent
External urethrotomy	59	33.5	188	20
Postoperative hemostasis	6	4.3	20	2.1
Transfusions	68	39	102	10.8
Mortality	2	1.1	12	1.3
Re-resection	5	2.8	31	3.3

Follow-up of all cases	Cases
Total cases	176
No replies	9
Replies	167
Deaths since leaving hospital (none due to prostatic disease)	10
Invalids—due to cerebral accidents since leaving hospital	4

There remain, then, 153 replies from patients who are at the present time living and active.

The question and the replies are summarized as follows:

1.	Do you now urinate normally without effort?	151
	Or, do you have to strain to urinate?	2
2.	Do you have any burning or pain on urination?	
	No	145
	Yes	5
	Sometimes	3
3.	Do you have complete urinary control? Yes	150
	If not, please explain. No	3

One patient had complete incontinence for 9 months—then began to regain his control and now—2½ years after operation—he has only stress incontinence. This patient had petressin-adrenalin mixture injected via the perineum to prevent operative bleeding. After operation, he bled severely for 4 days and nearly died as a result of hemorrhage. It is believed that the perineal injection, or else traction on the hemostatic bag, may have played a part in his postoperative incontinence.

The remaining 2 patients who lack complete control have stress incontinence so slight that it in no way interferes with their activities of life—in the conduct of executive affairs of business.

4.	Do you have normal day frequency? Yes	146
	No	7
5.	How many times do you urinate between bedtime and morning?	
	No times	42
	Once	65
	Two or three times	42
	Four times	4
	More than four times	0
6.	Is the urine clear?	125
	Is it cloudy?	23
	Sometimes cloudy	5
7.	Is your sexual function now more vigorous?	24
	Less vigorous than before operation?	28
	Is it unchanged?	93
	No reply to this question	12

TABLE V.—LATE FUNCTIONAL RESULTS

	Perineal prostatectomy	Resection
Total cases (consecutive)	100	100
Urinate too frequently (patient's own opinion)	15	17
Nocturia		
Not at all	20	45
Once	41	31
Two to four	33	23
More than four	6	1
Difficulty with urination	6	1
Result—(patient's own opinion)		
Well	89	90
Improved	10	9
Unimproved	1	1

TABLE VI.

Hospital Number	Age	Amount of tissue gm.	Do you void normally?		Burning or pain		Complete control		Normal day frequency		Nocturia					Sexual function			Urine		Comments
			Yes	No	Yes	No	Yes	No	Yes	No	0	1	2–3	4	Over 4	Increased	Less	Unchanged	Clear	Cloudy	
513769	79	129	+			+	+		+			+					+			+	
641730S	66	88	+			+	+		+			+					+		+		
68505S	70	160	+			+	+		+		+							+	+		
546122	65	128	+			+	+		+				+			+			+		
551256	73	80	+			+	+		+				+				+			+	
521738	63	124	+			+	+		+		+							+	+		
501228	73	84	+			+	+		+		+					+			+		
544298	71	87	+			+	+		+				+				+		+		
666845	53	94	+			+	+		+			+						+	+		
558865	82	136	+			+	+		+		+					No reply			+		
497864	69	91	+			+	+		+		+							+	+		
555380	83	80	+		+		+		+					+			+			+	
72041S	78	80	+			+	+		+				+					+	+		
502096	69	98	+			+	+		+			+						+	+		
61999S	58	88	+			+	+		+			+						+	+		
502190	68	120	+			+	+		+		+							+	+		
546656	81	80	+			+	+		+			+						+	+		
549868	75	90	+			+		+	+		+							+	+		Sl. stress incontinence
532504	69	83	+			+	+		+		+						+			+	
504224	65	115	+			+	+		+		+							+	+		
140060	67	130	+			+	+		+		+					+			+		
526539	76	155	+			+	+		+				+					+	+	+	Cloudy urine at times
323506	63	104	+			+	+		+		+							+	+		
530869	68	97	+			+	+		+			+					+		+		
520313	71	126	+			+	+		+		+							+		+	
289016	64	110	+			+	+		+		+					+			+		
541506	71	133	+			+	+		+			+				+				+	
64667	67	98	+			+	+			+		+						+	+		Day freq. 6 t.
553601	65	85	+			+	+		+			+						+	+		
518267	60	90	+			+	+		+				+				+		+		
527403	75	127	+		+		+		+			+					+		+		Sl. burning at times
527529	65	92	+			+	+		+		+					+				+	
509493	62	96	+			+	+		+			+					+		+		
54819	69	101	+			+	+		+			+						+	+		
61699	77	190	+			+	+		+				+					+	+		
542815	—	155	+			+	+		+				+					+		+	"Cloudy sometimes"
561194	58	113	+			+	+		+				+					+	+		
509062	—	124	+			+	+		+			+						+	+		

TABLE VI.—Continued

Hospital Number	Age	Amount of tissue gm.	Do you void normally?		Burning or pain		Complete control		Normal day frequency		Nocturia					Sexual function			Urine		Comments
			Yes	No	Yes	No	Yes	No	Yes	No	0	1	2–3	4	Over 4	Increased	Less	Unchanged	Clear	Cloudy	
506320	76	80	+			+	+		+				+					+	+		
531421	67	109		+		+		+		+			+				+		+		Had complete incontinence. Has regained most of his control. Has now stress incontinence.
406493	77	110	+			+	+		+			+						+	+		
501493	64	80	+			+	+		+			+						+	+		
497142	67	81	+			+	+		+			+					+		+		About normal day frequency
63944S	73	100	+			+	+		+				+					+	+		
554174	68	96	+			+	+		+				+					+	+		
503475	67	125	+			+	+		+		+							+	+		
542949	77	110	+			+	+		+		+					+			+		
501801	69	112	+			+	+		+		+							+	+		
Total			47	1	2	46	46	2	46	2	15	19	13	1	0	7	12	28	40	9	

Total cases, 53.
Total active cases reported, 48.
No replies, 2 cases.
Two deaths—1 of cerebral accident; 1 of cirrhosis of liver.
One patient has had recent cerebral accident and is bedfast.

On the basis of these data, it is evident that all the patients except one have had an excellent result of operation.

The present status of these patients is particularly significant when compared to the end results that were reported by Dr. Edwin Davis and myself in 1940 when we presented comparative follow-up data on two consecutive series of 100 cases. One group was operated upon by Dr. Davis and had perineal prostatectomies, while the other series was resected by the present writer—these patients had benign glands af all sizes. In that report the data in Table V appeared.

We have long been of the opinion—based upon clinical impressions rather than factual data—that the end-results following adequate transurethral resection are just as good if not better in patients who have prostates that are classified as "large" or "very large," as in those who have smaller glands, and the comparative clinical data afforded by the present investigation would seem to support this view. In fact, the majority of our poorest results have been in cases in which the resection operation has yielded less than 10 grams of tissue. In order to gain additional information on the question of the relation of gland size to the quality of end-result following resection, the data on the patients who had 80 grams or more of tissue removed at operation have been listed along with the details of their follow up reports Table VI. There were 53 such cases.

These data show conclusively that the "very large" prostates, i.e., glands yielding 80 to 190 grams by resection, have enjoyed end-results following operation that are just as excellent as the results in cases that involved the removal of lesser amounts of tissue. Moreover, among the 24 patients who had 100 or more grams of tissue removed there are but 6 who have nocturia 2 to 3 times while 8 have nocturia once, and 10 have none at all—surely substantial evidence to refute any contention that the quality of results following prostatic resection is adversely affected by the magnitude of the gland.

The matter of sexual vigor following prostatectomy is one that should be of consider-

able interest to all urologists, since many candidates for prostatectomy enjoy sexual potency and are interested in retaining it if possible. To be sure, many men in this age group have, for one reason or another, lost a participating interest but not a few are surprisingly active sexually, and the latter are often particularly anxious that this function be preserved. The urological literature is remarkably free from data upon the subject of the effect of prostatectomy on sexual vigor, and in general prostatectomists appear to show an indifference in the matter. Most surgeons express the belief that persistence of sexual vigor following perineal prostatectomy is most unusual while that following suprapubic enucleation is relatively commonplace. In the present series of 176 cases there were 93 patients who stated that they noted no change in potency following resection, while 28 had less and 24 an increase in sexual vigor. No replies to this question are available on the remaining cases. In the postoperative follow-up survey of 1940, the resection cases were interrogated regarding the matter of sexual potency. Among the one hundred consecutive cases in that series there were 24 who reported an increased sexual potency while 10 had a decrease and the remaining 66 patients observed no alteration in sexual vigor.

SUMMARY AND CONCLUSIONS

An evaluation of clinical data on 176 patients with "large" prostates treated by transurethral resection at the University of Michigan Hospital discloses the fact that gland size was not a determining factor influencing the morbidity, mortality, or length of hospital stay.

Comparison of data on this group of cases with those of all benign cases reveals that the blood losses are greater when the large glands are resected and as a result, that postoperative transfusions are more often required; also, that external urethrotomy is done more often in this group of cases, 33.5 per cent, than in all resection cases, 20 per cent.

The end-results following transurethral resection in this group of cases are considered to be excellent, with only one case that can be regarded as a poor result. The end-results in the patients having more than 80 grams of tissue removed were just as good as those of the other patients of this group, and these facts support the impression that has long prevailed among experienced resectionists: that patients with "big" glands enjoy just as good results following a proper resection as do patients having smaller prostates; that the quality of end-result following transurethral resection is determined not by the size of the prostate, but rather by the adequacy of its removal.

THE MANAGEMENT OF POSTOPERATIVE CHOLEDOCHOLITHIASIS

Another Use for Solution G

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THIS discussion is concerned with the specific problem of recurrent common duct stones as delineated by postoperative cholangiography; with a brief review of existing methods of treatment and a report of 2 cases in which solution G was effective.

Previous to the advent of cholangiography, the early diagnosis of postoperative recurrent choledocholithiasis was not often proved unless the obstructive symptoms of colic, jaundice, or biliary fistulas made reoperation imperative. Despite technical advances, such as the wider acceptance of the several variations of spinal anesthesia for improved and sustained abdominal relaxation, well illuminated and transilluminated operative fields, the practice of dilatation of the sphincter of Oddi with Bockus dilators and even irrigation and air suction of the common and hepatic ducts, a delayed cholangiogram provides the only assurance that stones are not left behind. Therefore, carefully evaluated roentgenologic study of the biliary tree is indicated before removal of the Kehr tube.

Immediate or operative and delayed or postoperative cholangiography are available. The latter method is preferred because it enables the radiologist to make the examination where there is ready access to all technical facilities including those for fluoroscopy. Here injections can be made into the T-tube and the medium followed visually as it passes through the ampulla into the duodenum. This is especially important in the final cholangiography.

Many types of radiopaque media have been used in outlining the biliary ducts. Bismuth paste and barium solutions were used by the earlier workers in this field, and more recently lipiodol, hippuran, potassium iodide, and potassium or sodium bromide have been employed. Diodrast and thorotrast have also been used extensively. It is beyond the scope of this paper to discuss the advantages and disadvantages of the various media. Diodrast, 30 per cent solution, has been used routinely and with satisfactory results. Caution should be used if there is a history of allergy, and suitable sensitivity tests may also be indicated.

The patient is placed on the roentgenographic table and, in the supine position, bile is aspirated by means of 30 or 50 cubic centimeter syringe. The ducts are then irrigated with 50 cubic centimeters of warmed normal saline solution. Sterile technique should be employed because of the possibility of extravasation of the solution or of the diodrast. The syringe is then filled with diodrast which has been previously heated to body temperature. Injection is made (10 c.c.) under roentgenoscopic guidance and spot roentgenograms made in the anteroposterior and oblique projections. An additional 10 cubic centimeters is then injected and another film is made, a Bucky diaphragm being used. A final injection is done and the last film is made in the oblique projection. If there is any delay in the dye entering the duodenum, films may be made at 15 minute intervals. Amyl nitrite or nitroglycerin may be given in case there is undue delay in duodenal filling in order to differentiate spasm from organic obstruction.

Postoperative common duct concretions develop from small nuclei of biliary débris or may descend from the higher hepatic radicals which are not reached by probe, suction, or irrigation. With the increasing practice of choledochostomy coupled with routine postoperative cholangiography, many more of

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these disappointing cases are certain to confront the surgeon. Best (3), Pibram, Torres, Best and Hicken (4) and Negri and Negri have made pointed reference to the importance of the problem and to its solution.

Reported methods of attack may be roughly classified as direct and indirect. Of the latter, Best and Hicken advocate the use of dehydrocholic acid and antispasmodic drugs by mouth and irrigation of the T-tube with sterile olive oil or lipoiodine. More recently, Best (3) has urged the use of "the three-day biliary flush regimen" before as well as after operation.

Torres reports the use of Pibram's method, but now prefers Best's procedures.

Pibram records successful results in 38 cases treated with ether instillations into the Kehr tube. This is followed by liquid paraffin by the same route. This direct method is based on the dissolution of cholesterol by ether, "and liquid paraffin helps to transform the stones into a soft pulp that can easily pass through the papilla of Vater."

Negri and Negri after encountering certain difficulties and inconveniences of Pibram's routine made a study of cholesterol solvents. *In vitro* studies indicated that Prevet's gomenol[1] easily reduces cholesterol and cholesterol pigments. *In vivo*, 1 case is reported after a preliminary instillation of 1 cubic centimeter of Merk's doryl (carbaminoylcholine) followed by gomenol 10 cubic centimeters daily for 10 days.

The attention of one of us (B.G.) was drawn to this problem by several unsatisfactory experiences. Before cholangiography was a routine postoperative procedure, the T-tube was removed at the end of 21 days, provided, after clamping, no colic ensued and the bile, urine, and feces were of normal color. After roentgenographic examination was applied postoperatively to all choledochostomies, several cholangiograms revealed stones in the common ducts. Operatively, these cases had been thoroughly explored, air suction applied, and a Bockus dilator passed into the duodenum. Treatment in the beginning was irrigation of the Kehr tube and duct with sterile normal saline and later Pibram's method was used. The latter was not always satisfactory, usually producing a great deal of pain for the reason that ether boils at body temperature. In one patient in whom a small leak was demonstrated to have developed around the T-tube, the injection of even 1 cubic centimeter of ether produced very obvious shock.

It is for these reasons that a search was made for some substance which would act directly upon the retained calculi and reduce them chemically.

The criteria for such a substance should be: (1) a liquid—one that is non-toxic and readily made or easily obtainable; (2) it must bring about chemical reduction of cholesterols and calcium salts.

The work of Suby and Albright (10) and others (1, 2, 5, 8, 9, 12) with solution G[2] in the dissolution of urinary calculi readily suggested itself since like urinary incrustations and concretions, gall-bladder and common duct stones also contain calcium. Best and Taylor[3] classify gall stones as: (1) "pure" cholesterol, (2) cholesterol-pigment-calcium, (3) "pure" bilirubin, (4) bilirubin-calcium, (5) calcium carbonate. Of these, bilirubin-calcium stones are the most commonly found variety and theoretically, solution G should be chemically effective on the greater proportion of common duct stones.

Before *in vitro* studies could be arranged, 2 patients were subjected to operation and upon postoperative cholangiography, were found to have retained common duct stones. Because Pibram's method of treatment failed in the first case, it was decided to try solution G upon empiric grounds.

CASE 1. Abstract of Hamot Hospital Record 68905. E.P., white female, aged 44 years, housewife, was admitted December 10, 1943, complaining of recurrent attacks of abdominal pain in right upper quadrant with occasional nausea, vomiting, and jaundice. Present attack was of several weeks' duration. Jaundice was present, sclerae were yellow, and definite tenderness was made out over the gall-bladder area. Temperature on admission was 100.2 degrees.

The clinical laboratory findings (admission studies) were as follows: Urine—reaction alkaline; specific gravity 1014; albumin, 20 milligrams; sugar,

[1]Gomenol—20% oil cajeput, 80% olive oil. Melaleuca virdiflora 20% is used. This is a species of cajeput.

[2]Solution G: Citric acid (monohydrated)..... 32.25
Magnesium oxide (anhydrous)..... 3.84
Sodium carbonate (anhydrous)..... 4.37
Water qs ad..... 1000 c.c.

[3]Best and Taylor, Physiological Basis of Medical Practice. P. 745. Baltimore, Md.: William & Wilkins ,1937.

Fig. 1.

Fig. 1. Case 1. Cholangiogram made on January 11, 1944, showing stones near the T-tube (see upper arrow) and an impacted stone in ampulla (see lower arrow). Note the dilated biliary ducts and the absence of dye in the duodenum.

Fig. 2.

Fig. 2. Case 1. Examination of January 15, 1944, following irrigations of duct. Stones still present. Small amount of dye in duodenum.

Fig. 3.

Fig. 3. Case 1. Final examination 2 weeks later. Stones have disappeared and dye readily enters the duodenum.

negative—microscopic triple and amorphous phosphates. Coagulation time of blood was 5 minutes. The blood count showed: hemoglobin, 84 per cent; red blood cells, 4,500,000; color index, .93; white blood cells 8,500; polymorphonuclears 76 per cent; small leucocytes, 20 per cent; eosinophiles, 2 per cent; mononuclears, 2 per cent. Blood sugar 81. Blood urea nitrogen, 11.1. Blood Wassermann and Kline, negative. Blood Icterus index 17.5 units. Blood van den Bergh direct, weakly positive, delayed indirect 3 milligrams. Cholecystograms—abnormal biliary tract—gall stones.

The preoperative preparation consisted of low fat diet, 5000 cubic centimeters of distilled water plus 5 per cent glucose, 1000 cubic centimeters of normal saline plus 5 per cent glucose—given over 48 hours. Operation was performed December 13, 1943. Spinal anesthesia and cyclopropane were administered with 2 cubic centimeters of spinocain injected between the 12th dorsal and 1st lumbar. The transverse approach was used. The gall bladder was found to be markedly distended, containing many stones of various sizes and some gravel-like material in the common duct. The cystic duct and cystic artery were separately isolated and ligated with No. 000 chromic—the gall bladder was removed from below upward. The common duct was incised, the hepatic and common ducts were explored, and a probe passed into duodenum. A T-tube was sutured into the common duct. No. 70 cotton was used to tie bleeding points, No. 32 Babcock wire—continuous figure of 8 stitch—to close peritoneum and fascia. No. 32 Babcock wire was used to suture subcutaneous tissue and subcuticular stitch of the same was applied to the skin.

Examination of the tissue revealed: chronic cholecystitis with cholelithiasis. Patient made an uneventful recovery. First cholangiogram, December 28, 1943, revealed radiolucent stones but dye entered the duodenum. The T-tube was irrigated with normal saline daily. No change was noted in the cholangiogram of January 6, 1944. Two and one-half cubic centimeters of ether was injected, the tube was clamped, and then irrigated with normal saline. Another injection of 5 cubic centimeters of ether followed by saline injection accompanied by "cold sweat and faintness of patient." Five hours later, patient, pale and shaking, complained of severe pain similar to preoperative pain. January 7, 1944, irrigations with saline were administered; patient complained of pain and cramps when the tube was clamped off. Cholangiogram on January 8, 1944, showed a stone in ampulla. Two 1 cubic centimeter injections of ether were given. January 9, 1944, three 1 cubic centimeter injections of ether were given. January 10, 1944, the same treatment was given in addition to magnesium sulphate 1 ounce by mouth. January 11, 1944, three 1 cubic centimeter injections of ether were given. A cholangiogram revealed no dye passing into the duodenum.

On the evening of January 11, 1944, the patient suffered considerable pain. A flask of 1000 cubic centimeters of solution G was set up to pass through a Murphy drip and the Kehr tube at the rate of 30 drops per minute. Pain continued for about 30 minutes. The apparatus was shut off and started again in another 30 minutes. Two hours later the patient stated she had a feeling of "fullness" but spent a fair night. One thousand cubic centimeters of solution G

was used during the day of January 12, 1944, there was occasional cramplike pain but she felt better and was able to be up and about throughout the day of the 13th, 14th and 15th. Cholangiogram of the 15th revealed the presence of the stones but dye slowly entered the duodenum. Two thousand cubic centimeters of solution G was administered on the 16th with little discomfort. The patient was able to be out of bed on the 17th. Stools on this day were green.

Cholangiograms taken on January 18, 1944 revealed absence of stones. Examination repeated January 19th revealed normal cholangiogram. No cramping had occurred during the last 3 days when the tube was clamped. The T-tube was removed on the 19th and the patient returned home. She reported by telephone the following day that the sinus had closed. She has been seen at 3 month intervals for 1 year and has reported excellent health. (Figs. 1, 2, 3.)

CASE 2. Abstract of Hamot Hospital Record 70124. E.G., white male, aged 49 years, was admitted February 9, 1944, complaining of upper abdominal pain, nausea, vomiting and slight jaundice. A history of similar attacks extends back to 1921. Appendectomy was done in 1921. Present examination revealed exquisite tenderness over the gall bladder; rebound reflex and jaundice present. Sclerae were noticeably jaundiced.

In preparation for surgery, 2 cubic centimeters of hykinone, and a transfusion of 500 cubic centimeters of whole blood were given. Operation was performed February 12, 1944. Cyclopropane-ether anesthesia was used; also transverse approach. The gall bladder was found to be markedly thickened, the ampulla bound down to the common duct. The common duct was dilated and thickened. Exploration of duct was done with a probe and air suction. No stones were found in the duct. Cholecystectomy and choledochostomy were performed. Wire closure was used. The report on tissue removed was subacute cholecystitis.

Patient made an uneventful recovery. First cholangiogram, February 24, 1944, demonstrated circular filling defect in common duct visible on all films. It did not obstruct the duct.

February 26, 1944, 1500 cubic centimeters of solution G were administered by Murphy drip to the T-tube; no reaction. Cholangiogram on February 29th revealed a normal finding. The T-tube was removed March 4, 1944. The sinus closed spontaneously March 7 and patient was discharged March 10, 1944. Patient has been seen in office every 3 months. There was no recurrence of symptoms.

The administration of solution G was borne by the patients without discomfort of any kind. They expressed the same opinion—a feeling of well-being after the instillation of the first 1000 cubic centimeters. There was no pain. A mild diarrhea occurred in Case 1, and in both the stools were green in color.

While the clinical results in the 2 reported cases were excellent, *in vitro* experiments, conducted later, results were disappointing when it was found that solution G per se and in admixture with bile, over a wide concentration range, had no apparent ability to dissolve biliary calculi of cholesterol type. Noted during experiments were bile flocculation and some change in appearance of cholesterol calculi surfaces but no perceptible weight loss.

Since these experiments indicate that solution G does not reduce cholesterol stones chemically, other explanations of its mode of action may be considered:

While the pH of liver bile varies between 8.0 and 8.6 and gall-bladder bile between 5.0 and 6.0, that of solution G is about 4.0. Such a solution might be sufficiently irritating to the mucosa of the common duct and sphincter of Oddi to activate the circular, longitudinal, and oblique unstriped muscular fibers found in these structures.

Since solution G so closely resembles liquor magnesii citratis (U.S.P.), might not the results be explained upon its cathartic action?

SUMMARY AND CONCLUSIONS

1. Recurrent choledocholithiasis is discussed from the point of view of the surgeon, radiologist and chemist.

2. A brief review of the literature referring to existing methods of treatment is presented.

3. Two case histories are cited in which solution G was effective.

4. Explanations of the possible mode of action of solution G in the common duct are suggested.

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MARCH FRACTURES

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MANY articles have appeared in the literature during the past 3 years on the subject of march fractures, and it is significant that the authors concerned were of the Army or the Navy Medical Corps. In peacetime these fractures rarely occur, but they increase rapidly in wartime, especially during that period in which the recruit goes through a basic training program which entails a great deal of drilling and marching. Because the lesion is so often precipitated during a march—46 per cent—it has been appropriately termed "march fracture," and even though many other names have been suggested from time to time, the term continues to appear traditional of these nontraumatic fractures of the metatarsals. Similar fractures are being reported in other bones, particularly the tibia, femur, fibula, os calcis, and more rarely in the pelvic bones and ribs; and they, together with the march fracture, are commonly referred to by J. B. Hartley's descriptive term "fatigue fractures of bone."

It is the author's purpose to report some observations made during the treatment of 58 cases of march fracture in the period from September 1, 1944, to February 10, 1945. All the patients were males who developed their trouble during some phase of their recruit schedule at a large Naval training center having a complement of 32,000 men.

First, it will be noted that the general data recorded in Table I parallel those of other authors and are therefore not considered unusual. However, the general body type encountered may reflect a slight glandular imbalance inasmuch as 57 per cent were either tall or fat; this finding, together with the low pulse rate—62—may signify, as will be pointed out later, a mild adult hypothyroid state. In this series only the second and third metatarsals were affected, there being no instances in which the first, fourth, or fifth were involved. One case is unusual in that the patient developed a march fracture in the second and third metatarsals, one following the other at an interval of 12 weeks (Fig. 1).

The opinions or assertions contained herein are those of the writer. They are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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ETIOLOGY

Many hypotheses have been advanced in the past to explain this lesion, and the following summary indicates that much uncertainty still exists as to its origin. We shall subdivide the various causes in the following manner:

I. Predisposing causes, *local*
1. Morton's syndrome (15, 12, 2, 3)
2. Inflammatory changes (16, 11, 18)
3. Vasospasm leading to bone atrophy (8)
4. Shoe gear irritation (14)
5. Decreased dorsiflexion of foot (1)
6. Muscle fatigue (17)
7. Spasm of intrinsic muscles (4)
8. Functionally weak foot (10)

II. Predisposing causes, *systemic*
1. Bacterial (5)
2. Neurologic disturbances (13)
3. Rheumatic diathesis (9)
4. Nutritional deficiencies (6)
5. Polyhypovitiminosis (19)
6. Mild hypothyroid state (ours)

III. Precipitating cause

This is generally agreed upon to be marching; or, according to Brandt, the result of "rhythmically repeated subthreshold mechanical insults acting by summation to a point beyond the capacity of the bone to bear stress."

Forty-eight of our 58 cases were studied from the standpoint of metabolic rate. The test was made after a 12 to 24 hour period of bed rest, and the average was found to be minus 10.72 per cent. The lowest reading recorded was minus 32 per cent, and the highest, plus 8 per cent. There were only 5 "plus" readings. Twenty-seven, or 56.2 per cent, were minus 10 per cent or lower; 15, or 31.2 per cent, had readings of less than minus 15 per cent; and 6 or 12 per cent, were below a minus 20 per cent metabolism. It is realized that great differences of opinion have arisen as to what constitutes the signs of hypothyroidism in cases not presenting the frank, typical picture of myxedema or cretinism; yet it is true that in adults we are forced to accept a lowered rate of metabolism as the most significant of the physical findings. A decreased rate cannot result from emotional disturbances, and it offers more reliable evidence of hypothyroidism than a high reading does of hyperthyroidism. The only associated symptoms of hypothyroidism and glandular dysfunction found

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 1. This patient suffered two march fractures 12 weeks apart. The older one involving the third metatarsal shaft is well healed. Periosteal callus is seen along the medial side of the second metatarsal shaft.

Fig. 2. A complete fracture line with displacement of the distal fragment.

Fig. 3. An incomplete fracture line involving the medial cortex of the third metatarsal, distal third.

Fig. 4. Faint periosteal callus on the medial side of the third metatarsal, distal third.

in our patients were the lowered pulse rate (average 62) and the fact noted above that 57 per cent were either tall or fat. There was no evidence of fatigue, weakness, nervousness, dry skin, or constipation noted. The relationship of a hypothyroid state to bone metabolism in an infant is clearly known, for if that deficiency has extended over a considerable span of time, the classical picture of cretinism will develop and skeletal changes, especially in the epiphyses, will occur due to a delay in the appearance of ossification in the cartilaginous centers. The relationship, however, between hypofunction of the thyroid gland and the skeletal physiology in adults is not clearly known; yet it may be that lesser degrees of osteoporosis develop if that deficiency is continued over a long period of time, as is the case in hyperpituitary and menopausal syndromes.

TABLE I.—GENERAL FINDINGS RECORDED IN 58 CASES OF MARCH FRACTURE

Number of males	58	
Average age in years	19.75	
Average height in inches	70.4	
Average weight in pounds	159	
Body types:	No.	%
Normal	25	43
Tall	30	52
Fat	3	5
Days in training before symptoms appeared—average days	41	
Precipitating causes:	No.	%
Marching	27	46
Obstacle course	24	41
Not known	6	10
Lifting	1	3
Degree of fracture:		
Complete	6	10
Incomplete (including those showing callus only)	52	90
Average pulse rate recorded in 33 cases—per minute	62	
Highest—per minute	80	
Lowest—per minute	44	
Metatarsal involved:	No.	%
Second	24	40
Third	35	60

THE CLINICAL COURSE

A variable amount of time elapses between the start of recruit training and the appearance of initial symptoms. That period may be from 7 to 105 days, which represents the extremes found in this group. The average lapse of time, however, is 41 days, and the first symptom is usually a burning pain which comes on in the course of a hike of 5 or more miles. The onset of that pain may be acute, 46 per cent, or insidious, 36 per cent. The remaining 18 per cent could not be ascertained. A characteristic limp parallels the pain, and these symptoms in turn are followed by soft tissue swelling on the dorsum of the foot. The severity of these cardinal symptoms (pain, limp, and swelling) increases for 7 to 10 days, when a plateau is reached in which they remain more or less stationary for 4 to 7 days. Following this stationary phase, improvement begins and, if untreated, will progress slowly for 14 to 21 days. These 3 phases in the course of a march fracture are both typical and constant, and they serve to determine beforehand the length of treatment which will subsequently be required. Ten, or 17 per cent, of the men were admitted during the first phase, 27, or 46 per cent, during the second phase, and 21, or 37 per cent, were admitted for treatment while in the improving or third stage.

The stages herein described are based largely on subjective findings obtained from the patients themselves, but are not free from occasional error if, for example, the man minimizes his symptom-

in order to "stay out of the sick bay." One must then be guided by the physical findings which are limp, localized tenderness, ability to walk on the tip-toes, soft tissue swelling, and the degree to which the long extensor tendons of the toes are obscured.

X-ray evidence of march fracture may not be forthcoming on an early plate, but is likely to appear after the 7th to the 10th day of illness. It has been our observation that roentgenologically the cases will fall into one of two major groups, so far as prognosis is concerned. The smaller group—10 per cent—is the most significant (Fig. 2), for here the fracture line runs completely across the shaft of the bone. The larger group—90 per cent—will either show an incomplete fracture line (Fig. 3), or simply a periosteal shadow (Fig. 4). We find it expedient to group the last two types together, as their response to treatment is usually the same.

TREATMENT

While there may be differences of opinion with respect to the etiology of march fractures, there is general agreement in regard to the treatment which conventionally consists of a short leg plaster-of-Paris cast for 3 to 5 weeks, followed by a period of physical therapy and a gradual return to weight-bearing, which requires an additional 2 to 3 weeks, making the period of total disability between 5 and 8 weeks. Simple strapping and the use of metatarsal pads have been tried, but the results are disappointing. Longitudinal metal bars and transverse Thomas bars applied to the shoe have also been used with slightly better results. Some have advocated bed rest in recent months, but as yet no report on the results of such treatment has been published.

Our routine entails the principle of bed rest for a period of about 5 days and the administration of desiccated thyroid (U.S.P.) 1 grain, three times daily. The patients are given bathroom (head) privileges and they are furnished crutches for this purpose. The amount of bed rest required where the fracture is complete will vary up to 9 days. An examination is conducted daily with particular respect to the soft tissue swelling, and it has been noted that the swelling will disappear gradually in 2 to 5 days, although the foot will appear swollen for many weeks, due to the presence of periosteal callus at the fracture site. It is important that one differentiate between these two (inflammatory and reparative) types of swelling. This can be done very easily by what our patients have come to call the "pinch test" (Fig. 5). By pinching the skin (over the second or third metatarsal heads) between the thumb and index finger on both the normal and affected feet, a thickening or turgidity in the subcutaneous tissue will be noted if inflammatory edema is present. In most cases this test will become negative at the end of the third, fourth, or fifth day. Bed rest is continued for 2 days after the pinch test is negative. The patient is then allowed up and returned to full duty with a supply of thyroid tablets sufficient to last a total of 19 days. No other treatment is given such as strapping, shoe corrections, or physiotherapy.

Fig. 5. "Pinch" test showing the soft tissue swelling on the left. Two days after this swelling has disappeared, the patient is allowed up. Swelling in the later stages of healing due to underlying periosteal callus is differentiated by this simple test.

RESULTS

In general the results obtained by this method have been exceptionally good as shown in Table II. The immediate results are 90 per cent good in that practically all the cases are symptom-free at the conclusion of the hospital stay; they are able to walk without pain or limp, and the "pinch" test is negative.

The intermediate results were recorded by periodic examinations throughout the first 2 weeks of duty. During this time no relapses or failures were encountered, although minor complaints were made by approximately one-half of the men. These symptoms were "plus-minus" in character; for example, "it doesn't bother me unless I double time too much," or "it hurts a little in the morning when I first get up," or "it felt funny the first few days after I left the hospital, but not enough to keep me from duty." These were typical comments in the patients'

TABLE II.—RESULTS OBTAINED IN THE TREATMENT OF 58 CASES OF MARCH FRACTURE BY BED REST; WITH AND WITHOUT THYROID MEDICATION

		No. of cases	Days of bed-rest Average	Results									
				Immediate (on leaving sick bay)		Intermediate				Final result			
						Those having minor but non-disabling symptoms for 1 to 14 days*		Those having no symptoms after date of discharge		Fair		Excellent	
				Fair	Excellent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
According to degree of fracture	Incomplete	52	5.25	7	45	23	45	29	55	2	4	50	96
	Complete	6	7.10	1	5	5	84	1	16	1	16	5	84
According to stage on admission	Getting worse	10	5.85	3	7	8	80	2	20	0	0	10	100
	Stationary	27	5.60	3	24	12	45	15	55	2	7	25	93
	Improving	21	5.20	2	19	7	34	14	66	1	5	20	95
According to thyroid medication	Given thyroid	24	5.66	2	22	9	37	15	63	1	4	23	96
	Not given thyroid	34	5.47	6	28	20	59	14	41	2	6	32	94

*Even the slightest complaint is recorded here, such as "occasional pain while running or jumping," or "pain on the first few steps in the morning." These symptoms were non-disabling in that full duty was continued and no further treatment was necessary.

own words, and indicate that the foot is not perfect after the period of bed rest, but in the absence of any objective signs, is capable of withstanding ordinary line of duty. Any extremes of exercise are likely to remind the patient of his recent injury. The intermediate results indicate the beneficial effect of the thyroid medication, for in those who received thyroid, there were no complaints in 63 per cent, while among those not receiving thyroid, only 41 per cent were symptom-free. This difference tends to corroborate our view that the systemic factor may be hypothyroidism.

The final results were uniform irrespective of all the variable factors; i.e., the use of thyroid and the stage of the lesion on admission made no apparent difference in the outcome. On the basis of 5 excellent and 1 fair result out of the 6 complete fractures, we may look to this group as the most uncertain.

SUMMARY

1. Fifty-eight cases of march fracture are presented, of which 48 were studied from the standpoint of basal metabolic rate. The average rate was minus 10.72 per cent. The average pulse rate was 62, and 57 per cent of the men were either tall or fat.

2. Bed rest for a period of 5 days and (in 24 cases) the administration of desiccated thyroid (1 grain three times a day) for a total of 19 days was the routine treatment followed.

3. A test is described which serves to differentiate inflammatory from periosteal swelling. This test is a guide in letting the patients up.

4. Mild, nondisabling symptoms were complained of in half of the patients thus treated (these symptoms lasted from 1 to 14 days).

5. Those who received thyroid showed better intermediate results than those who were treated by bed rest alone.

6. The final results were excellent, except for that group having complete fractures.

CONCLUSIONS

It is probable that a mild hypothyroid state may be a predisposing systemic cause in patients who develop march fractures. Cast treatment is not necessary, nor is it indicated except possibly in those cases in which the fracture line is complete. Bed rest continued through the period in which the inflammatory swelling is disappearing and continued for 2 days thereafter is the treatment of choice. The administration of thyroid substance for a short period is apparently helpful.

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FLUORESCEIN—ITS USE IN DETERMINING THE VIABILITY OF STRANGULATED INTESTINE

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IT may be stated that the diagnosis of viability of strangulated intestine has not been an exact science. As Wangensteen noted, "In borderline cases it is difficult to be certain by any method." Owings and Smith stated in reference to determining the safe point of resection, "The more experiments we did, the harder we felt this point was to determine with any degree of exactness." The potential viability of strangulated bowel has for the most part been estimated purely on a clinical impression based on return of color, pulsation of blood vessels, presence of peristalsis, and other signs found reliable by the individual operator.

Failure to diagnose, properly, damaged intestine carries a high mortality. The death rate in suspected strangulation with subsequent resection of doubtful bowel is three times as great as in those cases that escape resection (1). Until recent times no one has been able to remove the doubt in doubtful cases, while the obvious ones need little comment.

The use of fluorescein is a relatively new diagnostic aid that appears to be accurate and simple. Herrlin, Glasser, and Lange reported, as recently as 1942, the clinical use of fluorescein, among other diagnostic aids, in 4 cases of hernia and 1 of strangulated omentum. We wish to present 5 cases in which fluorescein was used at the Pennsylvania Hospital with satisfactory results. Its use clinched the diagnosis as well as furnished considerable information. It is a worth-while method of determining whether or not bowel is still viable. If there is a reasonable doubt about the viability of a segment of bowel whose removal would jeopardize a patient's life, the fluorescein method of evaluation is simple, safe, and accurate.

Fluorescein, a form of resorcinophthalein, is extremely diffusible (3). It also absorbs ultraviolet rays of long wave lengths. When these rays of 3,660 Angström units strike fluorescein, they are instantly converted into the longer light waves of the visible spectrum. In 1931, Lange and Wolheim (4) showed that this "fluorescence" could be demonstrated in living tissue. All that is necessary is a small amount of fluorescein in the circulating medium and the tissues glow, when exposed to ultraviolet light filtered with a Wood's type of filter. Chemically the dye appears inert in mammalian circulation. Pharmacologically, except for an unidentified interference with the activity of novocain and pontocaine, the dye is inactive and is excreted unchanged by the kidney, 99 per cent in 30 hours (1). The preparation of dye in use is a 5 per cent suspension of fluorescein in 5 per cent sodium bicarbonate solution having a pH of 5.7. The dosage is 20 cubic centimeters (1 gm.) of this suspension intravenously. We have observed no untoward reaction in over 50 cases.

Depending on the circulation time, the subject will be seen rapidly to "fluoresce" (90 seconds) by the time the eyes are accommodated. The degree of fluorescence depends on the type of tissue and amount of pigment present. The skin shows up quite well in normal white persons, poorly in the colored race. The mucous membranes and serous surfaces in both races show up equally well.

Inspection of the serosa of normal bowel exposed to filtered ultraviolet light when fluorescein has not been injected revealed coloring that is uniform. The intestine is dark purple, with a smooth velvety consistency. In marked contrast, the presence of fluorescein in the bowel makes the serous surfaces under the filtered ultraviolet light glow greenish gold with release of visible light that will even illuminate structures immediately adjacent. Bowel that has been temporarily or permanently deprived of its blood supply appears, when exposed to this light, an even deep velvety purple. The contrast between this deep hued area and the brilliantly glowing greenish golden bowel is dramatic and colorful. Similarly, when circulation returns and viability is restored, the gradual conversion of the dark purple velvet of the doubtful areas to a glowing golden state is unmistakable and astonishing.

On the basis of Lange and Boyd's work, who showed that fluorescence readily occurs where

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viability is present (3) and that it fails to occur when irreversible change has taken place, fluorescein was used in 5 cases. Each one presented a loop of small bowel so involved as to have a doubtful reversibility state.

CASE REPORTS

CASE 1. H. R., white male, 57 years of age, was admitted to the Surgical Service A of the Pennsylvania Hospital on January 14, 1944. Two days prior to admission a hernia, which he had had for years, descended into the scrotum and he was unable to reduce it. Since that time he had vomited twice, and three times on the day of admission. He stated that his abdomen had been "puffed up" with terrific pain for 2 days. There were no bowel movements for 3 days. Physical examination revealed an irreducible, indirect, inguinal hernia on the right side which was quite tender. No peristaltic sounds were heard over the firm scrotal mass. The overlying skin was red and edematous. The abdomen was slightly distended with a few high pitched tinkles.

Under continuous spinal anesthesia a constricting peritoneal ring was found. The strangulated portion of small bowel was delivered, the color of which was not satisfactory. Fluorescein was injected intravenously. Initially there was no fluorescence in the constricted bowel. However, at the end of 20 minutes the bowel was replaced in the abdominal cavity as fluorescence was seen to occur throughout the entire loop of doubtful bowel. Herniorrhaphy was completed. The postoperative course was benign and patient was discharged on the 14th postoperative day.

CASE 2. V. P., a white male, 58 years of age, was admitted to the Surgical Service A of the Pennsylvania Hospital on January 28, 1944. His chief complaint was painful hernia in the left groin for 2 weeks. He had had no bowel movements for 2 days. He was nauseated on the day of admission. Physical examination revealed the abdomen soft but high pitched peristaltic tinkles were heard throughout; no peristaltic rushes. In the left inguinal area there was a hard mass 6 centimeters in diameter with some redness over the overlying skin. The mass was irreducible and and there was no peristalsis over it. The preoperative diagnosis was strangulated inguinal hernia.

At operation a sac was found under Poupart's ligament which contained 12 centimeters of dark red bowel. Fluorescein was injected intravenously. No fluorescence occurred in this loop of bowel at first but in a few minutes fluorescence was seen to spread gradually over the entire doubtful area. The loop was returned to the peritoneal cavity and the hernia was repaired. The postoperative diagnosis was incarcerated femoral hernia.

After operation patient's general condition was excellent. A small hematoma developed in the wound but it resolved itself gradually.

CASE 3. M. K., a white girl, 14 years of age was admitted to the Lying-In Division of the Pennsylvania Hospital on August 9th, 1944, with a history of colicky pain around the umbilicus. The most recent attack of pain occurred 2 days before admission and was accompanied by nausea and vomiting. There was no referral of the pain. Physical examination revealed an extremely ill patient with a temperature of 103 degrees. The abdomen was slightly distended with generalized tenderness present. Peristalsis was hypoactive. A mass was palpated in the right upper quadrant and in the right adnexal region. The preoperative diagnosis was twisted ovarian cyst.

At operation a large intussusception was found and reduced. The damaged bowel, which was terminal ileum, with a polyp about 6 centimeters from the ileocecal valve, was atonic, purple, and filled with fluid. A foul odor was present. Exposure to a Wood's lamp after fluorescein was injected intravenously showed no fluorescence after 20 minutes of supportive treatment. The bowel was resected and repaired by a side-to-side anastomosis. For the first 48 hours after operation, toxemia was evident and the patient's progress was very stormy. She improved gradually and was discharged on the 14th postoperative day.

The pathological report was that the segment of ileum removed showed gangrene with a gangrenous polyp causing intussusception.

CASE 4. J. S., a white male, 61 years of age, was admitted to Surgical Service A of the Pennsylvania Hospital on November 16, 1944. The patient gave a history of hernia for 2½ years. This hernia was not associated with pain until 4 months ago. At this time, the hernial mass descended into the scrotum and could not be reduced readily by the patient. His own physician succeeded in the reduction, and there was no more pain until the day of hospital admission. Four hours previous to the time the patient was seen at the hospital, he complained of great pain in the scrotum. He also vomited. This pain was described as continuous and unrelenting in character.

At physical examination the abnormal findings consisted of a large tender mass in the right scrotum. Peristalsis in the abdomen was fairly active. There was some tenderness in the right lower quadrant of the abdomen. The preoperative diagnosis was strangulated indirect inguinal hernia.

The patient was operated on 3 hours after admission. The hernia was reduced and the involved bowel proved to be dark purple, edematous, and contained some thrombosed blood vessels. Damage was obvious. One gram of fluorescein was injected intravenously. Exposure of the bowel to Wood's filter did not at first reveal fluorescence. However, in 10 minutes, fluorescence was readily visible although not as evident as that appearing in normal bowel. With a diagnosis of viable bowel, the loop was returned to the abdomen and the herniorrhaphy completed. The postoperative course was uneventful and patient was discharged on 14th day.

CASE 5. R. P., a colored woman, 41 years of age, was referred from the Maternity department of the Pennsylvania Hospital on December 12, 1944 to Surgical Service A because of colicky pain in the abdomen, nausea and vomiting. She had had increasing distention and constipation. The patient gave a history of having had a hernia in the left groin which had reduced itself spontaneously 2 days previously.

At physical examination the abdomen was found to be distended and very little peristalsis was heard. Marked generalized tenderness was present especially over the left lower quadrant of the abdomen, where a mass was palpable. The patient experienced marked pain when the left inguinal region was palpated. Pelvic examination revealed a large firm mass in the cul-de-sac.

After the abdominal wall was opened, the posterior rectus sheath and peritoneum were found to be quite thickened and edematous. Bloody fluid and a loop of necrotic bowel presented in the peritoneum. The lesion was a volvulus of the terminal ileum with its base at the opening of the hernial sac. Fluorescein study showed absolutely no viability in approximately 16 inches of bowel even after 20 minutes of supportive treatment. The compromised bowel was resected and a side-to-side anastomosis was done.

After operation there was small rise in temperature and pulse on the 2d and 4th postoperative days. The hernia was repaired on the 14th day after the resection of damaged ileum. Microscopically, all sections showed marked hemor-

rhage and destruction of normal tissue architecture. Only a few muscle elements were still identifiable.

In none of the 5 cases was fluorescence visible in the involved loop of bowel at first inspection. After treatment, for no longer than 20 minutes in any case, with the usual supportive measures, the bowel was seen to "fluoresce" in 3 patients. These loops of bowel were diagnosed as being viable and were returned to their respective abdominal cavities. No fluorescence was observed in the two obviously gangrenous loops of bowel which were resected. Microscopic sections of the bowel showed necrosis of all the coats of the bowel wall in both cases. In one (H. R.) of the unresected cases, an area of nonfluorescent bowel in the damaged loop was found to be caused by a subserosal hemorrhage with glowing bowel wall demonstrable beneath the dark portion.

SUMMARY AND CONCLUSION

Five cases are reported in which fluorescein has been injected intravenously and an ultraviolet lamp with a Wood's filter was used to determine fluorescence in damaged bowel. The presence of fluorescence was sufficient evidence of viability to permit return of these damaged loops of bowel to the abdominal cavity. The absence of fluorescence was diagnostic of nonviability confirmed by microscopic section.

Postoperative course and pathological sections seem to bear out the prognosis based on the fluorescein method.

There seems to be adequate evidence that this relatively simple method removes the uncertainty from a diagnosis which never has been classified as exact.

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STRUMA LYMPHOMATOSA, STRUMA FIBROSA AND THYROIDITIS

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THE large proportion of cases reported under the general heading of chronic thyroiditis are of a nonspecific or unknown etiology. In the various subgroups of nonspecific chronic thyroiditis, namely struma lymphomatosa (Hashimoto), struma fibrosa (Riedel), and the pseudogiant cell type, or struma granulomatosa (De Quervain), there are no single pathognomonic or distinguishing features. The result has been a marked confusion in the literature where names have been used loosely without precise clinical and pathological description. It is our opinion that struma lymphomatosa is a clinicopathologic entity. Struma fibrosa and its pseudogiant cell variant are different manifestations of the thyroid's response to inflammation. These two groups are considered separately only to emphasize their essential similarities and relationships.

The general subject was touched upon during the Eighteenth Century with descriptions of suppurative and nonsuppurative thyroiditis (10). Later there were distinctions drawn between inflammation of a normal thyroid and a goitrous thyroid. In 1878 Kocher claimed that all inflammation of the thyroid was of a metastatic origin. In 1884 Bowlby, at the Pathological Society of London, presented a case of infiltrating fibroma of the thyroid, concluding that it was of a malignant and sarcomatous character. De Quervain (13) in 1904 stated that nonpurulent thyroiditis was a disease, *sui generis*, with definite clinical and pathological characteristics. Riedel (52, 53) in 1896, 1897, and 1910 described the extreme fibrosis and adjacent adhesions of the thyroid gland under the heading of *Eisenharte Strumitis*. Hashimoto, in 1912, described a diffuse enlargement of the thyroid gland by lymphocytic infiltration and lymphocytic hyperplasia, with accurate clinical and pathological descriptions. This he considered an entity, and not related to Riedel's *Eisenharte Strumitis*. Dr. Ewing in 1922 believed that lymphoid infiltration and hyperplasia, and fibrosis of the thyroid were the early and the late states of the same disease process, which he designated benign granuloma of the thyroid. Without reference to Ewing's opinion Williamson and Pearse (62) first in 1925 described a lymphadenoid goiter, similar to the descriptions of Hashimoto. Graham and McMullagh (25) in 1931 in a complete review of the literature with additions of cases of their own, separated the diseases as described by Hashimoto and Riedel into clinicopathological groups. This cast a shadow on Ewing's widely accepted opinion of 1922 and 1928.

During the next decade there was a great deal of confusion in the literature with supporters for and against the unitarian concept of etiology as expressed by Ewing. However the excellent reviews of Clute *et al.* (7) in 1935, and McClintock and Wright in 1937, Joll in 1939, Harry in 1940, and McSwain and Moore in 1943 together with numerous authors reporting cases, now support the balance heavily for clinical and pathological distinction between struma lymphomatosa and struma fibrosa.

At present many cases, reported as struma fibrosa are confused with the more acute and granulomatous form of chronic thyroiditis so beautifully described by De Quervain and Giordanengo (14) in 1936. They reported 8 cases of subacute and chronic thyroiditis of a nonspecific etiology. They traced the various stages of acute to subacute to chronic thyroiditis. The latter is characterized by many cellular aggregates resembling foreign body cells, acute and chronic inflammatory cell infiltration, acinar degeneration, and obliteration with marked fibrosis. This confusion is justifiable as struma fibrosa seems to be a late state of the earlier, more acute forms, which may resolve, or may be progressive in their pathological changes.

CASE REPORTS

Struma Lymphomatosa

CASE 1. No. 92994, A. W., 30 year old white female housewife, was first admitted to the Strong Memorial Hospital on May 24, 1938. Her chief complaint was rapid growth of her goiter, associated with dysphagia and nervousness of 3 months' duration. She had noted a moderate enlargement of her goiter for 14 years. Past history revealed diphtheria, pneumonia, tonsillectomy, saphenous vein ligation, 3 self-induced abortions, and 1 normal full term pregnancy. There were no coexistent diseases. Laboratory tests showed her white blood count to be 8,650; basal metabolic rate, 2 per cent; Wassermann negative. Physical examination re-

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vealed a well developed and nourished female. Temperature, pulse and respirations were normal. Blood pressure was 120/70. The thyroid was firm and diffusely enlarged, not tender, with no tracheal tug on swallowing. There was a nodule in the right lobe.

At operation a right subtotal lobectomy was performed. No adhesions were noted. Grossly the excised tissue was firm, tough and cellular, measuring 3 by 2 by 1 centimeter. Microscopically, there was an increase in fibrous tissue and marked lobulation of the gland. There was acinar degeneration with low flat cuboidal epithelium, little or no colloid, and small size of acini. There was a diffuse infiltration with lymphocytes and numerous lymph follicles with germinal centers. Postoperative course was uneventful. At follow-up, 9 weeks after operation further enlargement of left neck was noted. Basal metabolic rate at that time was —16 per cent and there were early signs of myxedema. Shooting pains in her forehead were noted.

The patient was readmitted April 9, 1939 because of tightness about neck, dysphagia and choking. At that time a marked diffuse enlargement of the left lobe and isthmus of the thyroid was noted. Basal metabolic rate was —23 per cent, cholesterol 162 milligrams per cent.

A left subtotal lobectomy revealed a firm fibrosed lobe which overlay the trachea anteriorly without adhesions. Grossly the excised tissue was tough and fibrous. The microscopic picture was almost identical with the first sections 11 months previously, except that the lymph follicles with germinal centers were more discrete, there was less general lymphocytic infiltration, and a moderate increase in connective tissue. Postoperative convalescence was uneventful with marked relief of obstructive symptoms. Myxedema was controlled by 60 to 90 milligrams of thyroid extract orally each day. Seven years after 1st admission 200 milligrams of thyroid extract was necessary each day. Otherwise in good health.

Case 2. No. 138258, V.K., 27 year old white female housewife, was first admitted to the Strong Memorial Hospital in March, 1938. Her chief complaint was of tightness in her neck and dysphagia of slowly progressive nature of 5 years' duration. Five years previously at another hospital she had had an enlarged isthmus of her thyroid removed with the pathological diagnosis of chronic thyroiditis and cellular hyperplasia. Unfortunately their microscopic sections were destroyed. Past history was negative. She had had one normal pregnancy. Laboratory tests showed her white blood count to be 7,200; Wassermann negative; no basal metabolic rate taken. Physical examination revealed a well developed and nourished female. Temperature, pulse, respirations were normal. Blood pressure was 110/70. Findings were negative except for a hard diffuse enlargement of both lobes of the thyroid, more marked on the right.

At operation bilateral subtotal thyroidectomy was performed. The only adhesions noted were at the site of the old midline scar. Grossly the gland was two to three times normal size, firm, grayish-yellow, with little bleeding. Microscopic examination revealed a diffuse lymphocytic infiltration with numerous lymph follicles with germinal centers. There was only slight increase in fibrous tissue. There was marked acinar atrophy, and the colloid was very scanty. Postoperative course was uneventful.

At follow-up 4½ years later a ureteral stone was removed transperitoneally. Five and a half years later basal metabolic rate was +4 though symptoms and signs of mild myxedema were noted which were controlled on 30 milligrams of thyroid orally a day.

Patients in Cases 1 and 2 were operated on twice. In Case 1 the microscopic sections 11 months apart are almost identical and are reproduced here. In Case 2 the microscopic sections of the first operation 5 years previously at another hospital were unfortunately lost. The microscopic diagnosis at that time of chronic thyroiditis and cellular hyperplasia, however, infers that little if any change occurred in this gland during the 5 year interval. These cases may be added to those of Perman and Wahlgren, Roulet, Clute *et al.* (7), McClintock and Wright, Joll, Hellwig and Heyd. Each of these authors reported a case in which no essential microscopic change from the original picture had occurred over periods up to 9 years. Heyd stated that his original microscopic section revealed struma lymphomatosa, and the second operation revealed struma fibrosa, thus confirming Ewing's beliefs. However, on review of his material, there seems little question that the first operation on the patient revealed a struma fibrosa, and that there was actually no transition, except in degree of fibrosis and adhesions.

Case 3. No. 69460, E. A., white female housewife, was admitted for the third time to the Strong Memorial Hospital in June 1943. Her chief complaints were of pressure on neck, gradual increasing fullness of neck anteriorly, and dyspnea of 2 years' duration. She had been followed a year by her private physician before admission for surgery during which time the symptoms were slowly progressive. Past history revealed tuberculous adenitis 10 years previously. Toxemia of pregnancy occurred 4 years prior to admission with termination of pregnancy by cesarean section and hysterectomy.

Laboratory examination showed white blood count to be 8,400; basal metabolic rate —18 per cent; Wassermann, negative. Physical examination revealed normal temperature, pulse and respiration; blood pressure of 120/70; and was negative except for a firm diffuse enlargement of the thyroid gland two to three times normal size.

At operation bilateral subtotal thyroidectomy was performed. Grossly the tissue excised was uniformly firm and finely lobulated. Microscopic examination showed a diffuse lymphocytic infiltration with numerous lymph follicles with germinal centers, a slight increase in connective tissue, marked acinar degeneration with scanty colloid. Postoperative course was uneventful. At follow-up 4 months after operation, basal metabolic rate was —27 per cent with signs and symptoms of early myxedema. At present, December, 1944, she controls her symptoms with 30 to 60 milligrams of thyroid extract orally each day and is in otherwise excellent health. She has noted that less thyroid extract is necessary now than immediately after operation to control signs and symptoms of myxedema.

Case 4. No. 161525, L.S., 52 year old white male, was first admitted to the Strong Memorial Hospital in January, 1940. The chief complaint was a lump in neck and hoarseness of 7 months' duration. He also noted paresthesias of extremities. He was afflicted with a rare skin condition, pseudoxanthoma elasticum, and had the associated angioid streaks of the retinas with progressively failing vision. Past history was essentially negative. Family history revealed a sister with a similar skin lesion.

On physical examination temperature, pulse, and respiration were normal; blood pressure was 160/85. There was a loss of elasticity of the skin of the upper trunk and neck.

and it was thickened. There was a diffuse enlargement of the thyroid most prominent in the midline.

At operation excision of enlarged isthmus only was carried out but no adhesions were noted. Grossly the excised tissue was smooth, firm, tough, with a yellowish cast. Microscopic examination revealed a diffuse infiltration with lymphocytes and numerous lymph follicles with germinal centers. There was a moderate increase in connective tissue, particularly in interlobular septa. There was almost complete absence of acinar epithelium. There were rare plasma cells. There were rare intra-acinar cellular aggregations resembling foreign body giant cells. Postoperative course was uneventful. Patient received 800 r of deep x-ray to right and left anterior cervical regions. At follow-up basal metabolic rate shortly after operation was —33 per cent. The thyroid gland melted away in size following x-ray, and 1 month later the neck had decreased over an inch in circumference. The patient developed mild signs and symptoms of myxedema and was controlled on 60 to 90 milligrams of thyroid extract orally each day. At the time he was last seen he was almost blind from progression of the retinal lesions in both eyes. He died at the Veterans Hospital in 1942, and the report is as yet unavailable.

Case 4 is a male with struma lymphomatosa and one of the few ever to be reported. He is also interesting in that he had one of the rare skin lesions, pseudoxanthoma elasticum, coincidentally. This man exhibited all the clinical and pathological characteristics of struma lymphomatosa, including an excellent response to x-ray. He developed marked myxedema, even though only the enlarged isthmus of his thyroid was removed. Graham (26) in 1931 reported 2 males, Joll reported 3 males, and Kearns reported 1 case of a male with struma lymphomatosa.

Case 5. No. 94097, C.S., 28 year old white female housewife, was admitted for the second time to the Strong Memorial Hospital in November, 1935. Her chief complaint was of moderate diffuse enlargement of her thyroid for 7 years and rapid growth for the last 2 months with pain and tenderness on the left. There was rather marked associated dyspnea and dysphagia. Basal metabolic rate 1 year before entry had been —10 per cent. Past history was negative except for a mild depressional psychosis a year prior to admission. She had had 2 normal pregnancies; no coexistent diseases.

Laboratory examination showed basal metabolic rate of —9 per cent; Wassermann reaction was negative. Physical examination revealed normal temperature, pulse and respirations; blood pressure 122/80. The thyroid was diffusely enlarged and more so in the isthmus. It was hard and tender.

At operation bilateral subtotal thyroidectomy was performed with rather marked difficulty because of adhesions to the soft tissues of the neck. Grossly the gland was finely nodular, tough, firm to hard.

Microscopic examination revealed a moderate to marked increase in fibrous tissue. There was almost complete acinar degeneration with little or no colloid. Many acini had coalesced into pale foamy type of cells without resemblance to foreign body giant cells. There was a diffuse infiltration of lymphocytes with numerous lymph follicles with germinal centers. There were a moderate number of plasma cells. A rare pseudogiant cell was seen. Postoperative course was uneventful. At follow-up examination basal metabolic rate 2¼ months later was —30 per cent. Three and a half months after operation a thyroid graft from another patient undergoing thyroidectomy was implanted directly on the femoral vessels in the left groin beneath the inguinal ligament. Though apparently this graft was viable temporarily it was completely unsuccessful and at 4½ months there were unmistakable signs of myxedema, and the basal metabolic rate was —35 per cent. The patient has been followed since for 9 years with basal metabolic rates ranging from —30 to —40 per cent. The blood cholesterol at one time was 300 milligrams per cent. Except for recent menopausal symptoms now at the age of 37 years, the patient feels well and is controlled on 120 to 200 milligrams of thyroid extract each day. Neck is soft, nontender, and there are no pressure symptoms.

Case 5 is an enigma. She presents characteristics that make difficult her classification. Good evidence for struma lymphomatosa is her past history of diffuse enlargement of her thyroid with a low basal metabolic rate, the gross appearance of the preserved specimen, the microscopic appearance of the gland, her postoperative course of myxedema, and her early menopause. One suspects the diagnosis of struma fibrosa because of her age, recent acute history superimposed on a chronic enlargement, rather marked pressure symptoms, adhesions of the thyroid at operation, and rather marked fibrosis of the gland. This may be explained by a subacute nonspecific inflammatory reaction superimposed on an already existing struma lymphomatosa. With regard to Case 5, it should be noted that there was an unsuccessful attempt at a homologous type of thyroid graft, in an effort to control her progressive, postoperative myxedema.

Case 6. No. 140044, M.W., 15 year old white school girl, was admitted for the fifth time to the Strong Memorial Hospital in September, 1944. Her chief complaint was diffuse enlargement of the thyroid for several years, with associated recent hoarseness, slight dysphagia, and dyspnea. She also noted occasionally sharp pain in her right neck that radiated to her right ear. Growth of her gland had been rapid 3 months before entry. Her basal metabolic rate had been around —5 per cent for the 6 year period prior to admission. Two cholesterol determinations were 185 and 206 milligrams per cent. Two years before admission she had received sporadically a little potassium iodide and thyroid extract by mouth. Her past history revealed tonsillitis 6 years before present admission at which time a diffusely enlarged goiter of moderate size was noted. Other admissions were for tonsillectomy, otitis media, and abdominal pain. At the latter admission the thyroid was somewhat tender to palpation and the question of acute thyroiditis had been raised.

Laboratory examination showed cholesterol 180 milligrams per cent; basal metabolic rate —19 per cent; Wassermann reaction was negative. Physical examination revealed a moderately obese girl, blood pressure 120/70; temperature, pulse, and respirations normal; otherwise negative except for a diffusely enlarged firm gland without fixation. The gland was about three times normal size.

At operation biopsy of isthmus only was done. No adhesions were noted. The tissue was grossly firm, with a yellowish cast on cut surface. Microscopic examination showed a moderate infiltration of lymphocytes throughout the stroma among the acini with numerous lymph follicles and

germinal centers. The acini were for the most part large and filled with colloid. The acinar epithelium was flattened and very low cuboidal type. There was a slight interlobular increase in connective tissue. Rare plasma cells were seen. No giant cells were seen. Postoperative course was uneventful.

She received immediately after operation 800 r deep x-ray therapy to the right and left anterior cervical regions over her thyroid. Within 2 weeks her thyroid had decreased markedly in size with relief of symptoms. Six weeks after radiation her thyroid had increased to former size. Accordingly a second course of x-ray was given; 600 r were directed at the right and left anterior cervical ports. Her response again was immediate, with a 50 per cent reduction in size of the gland in 2 weeks. Two months after operation, her basal metabolic rate was —13 per cent. Five months after operation her thyroid was 50 per cent its original size and she was having menstrual irregularities. She was started on thyroid extract, 65 milligrams a day orally. August, 1945 the patient's menses are regular, and her thyroid gland though palpable is 25 per cent of its original size and asymptomatic.

Case 6 is one of the youngest cases reported of struma lymphomatosa. Joll mentions a girl aged 10 years, Bogart mentions a negro girl aged 14 years, and Hellwig presents a case of a 16 year old girl. The question may justly be raised in this case as to whether this might not be an adolescent colloid goiter with focal areas of lymphoid hyperplasia. The work of Simmonds (57) showed that 40 per cent of simple colloid goiters between the ages of 10 and 20 years revealed, on microscopic section, areas of lymphoid hyperplasia. This fact leads one to scrutinize the diagnosis of struma lymphomatosa closely in any very young adult. However, the relatively long history with recent rapid enlargement, the tendency to myxedema, moderate pressure symptoms out of proportion to the size of the gland, shooting pains to her right ear, the surgical and gross appearance of the isthmus, the diffuse enlargement, and the great number of lymph follicles with germinal centers, support the diagnosis of early struma lymphomatosa. Her response to x-ray further corroborates the diagnosis.

Struma Fibrosa

Case 7. No. A1236, A.vK., 57 year old white female housewife, was admitted the second time to the Strong Memorial Hospital in August, 1930. Her complaint was of vaginal bleeding and dyspnea. The thyroid had been increased in size and variable in shape, size, and hardness for the past 12 years. She had coexistent carcinoma of the cervix with pelvic metastases and necrosis which caused death shortly after admission. Terminally her dyspnea became quite acute but was not a noticeable feature early on admission. At postmortem examination, the thyroid was diffusely enlarged and bone-like in consistency. It was so densely adherent to the trachea and had grown around the esophagus in such a manner that it was fortunately dissected *en bloc* and preserved as a museum specimen.

Microscopic examination showed complete fibrosis of the gland with a compression of an adenoma in one lobe. There was very little thyroid tissue seen in any of the sections but where noted the acini looked fairly normal. Moderate numbers of lymphocytes were seen and a rare polymorphonuclear cell. No pseudogiant cells were seen. An occasional plasma cell was present.

Case 8. No. 218923, A.K., 37 year old white female housewife, first admitted to the Strong Memorial Hospital in May, 1944. Her complaint was of occipital headaches, choking sensations, and emotional turmoil of 1 year's duration. Past history revealed a question of carcinoma of the cervix with treatment by small amount of x-ray and an excision of an ovarian tumor at an outside hospital. She had had 3 normal pregnancies, and had had marital difficulties.

Laboratory examination showed a white blood count of 7,600, Wassermann reaction was negative. Physical examination showed normal temperature, pulse, and respirations; blood pressure 92/50. Thyroid was stony hard, diffusely enlarged, and nontender.

At operation bilateral subtotal thyroidectomy was performed. There were dense adhesions requiring sharp dissection and the resection was performed with great difficulty. Grossly the tissue was hard and cartilaginous in consistency. Microscopic examination showed almost complete replacement of thyroid tissue with fibrosis of a hard and hyalinized nature. Acini were fairly normal in appearance where present. Numerous lymphocytes, plasma cells, and polymorphonuclear cells infiltrated in the fibrous planes. An occasional pseudogiant cell was seen. Postoperative course was uneventful.

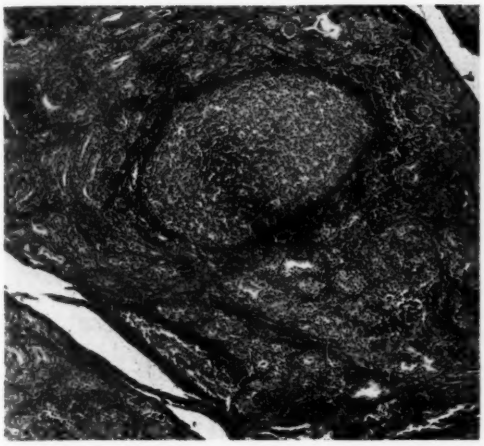
At follow-up examination 3 weeks after operation basal metabolic rate was —28 per cent. The patient was readmitted in 2 months for signs and symptoms of mild tetany. Her blood calcium was 5.4 milligrams per cent and her blood phosphorous was 3.0 milligrams per cent. She was readily controlled on calcium chloride solution 8 cubic centimeters three times a day and 50,000 units of vitamin D each day. At discharge her calcium and phosphorous levels were 10.4 and 6.0 milligrams per cent, respectively. Five months after operation her blood calcium and phosphorous levels were 8.2 and 5.6 milligrams per cent and she was controlled on 100,000 units of vitamin D each day and calcium gluconate 4 cubic centimeters three times a day. There is hardness over the lateral aspects of each lobe of her thyroid which could not be resected, but there is no tenderness. She has no dysphagia and dyspnea and her trachea can be easily felt with no overlying tissue.

Struma Fibrosa—Giant Cell Variant

Case 9. No. 20284, M.V. 35 year old white female housewife, was first admitted to the Strong Memorial Hospital in January, 1939. Her complaint was of sharp recurrent pain with a swelling in the right neck, and slight dysphagia and dyspnea of 1 month's duration. Past history was completely negative. She had had 6 normal pregnancies.

Laboratory examination showed a basal metabolic rate of 0 per cent, white blood count of 9,650, negative Wassermann, trachea compressed in the x-ray film. Physical examination revealed normal temperature, pulse, and respirations, blood pressure of 120/80. The right lobe of the thyroid was four times normal size, very hard, and fixed to the surrounding tissues. The left lobe was normal.

At operation right subtotal lobectomy was done. The right lobe was densely adherent to the surrounding soft tissues. The left was normal in appearance and to palpation and was not disturbed. The right was firm, white, hard. Microscopic examination showed a very marked increase in fibrous tissue, with areas of lymphocytic and occasional plasma cell infiltration. The acini were compressed and many appeared fairly normal, though an equal number were degenerate and had coalesced into pseudogiant cells. Postoperative course was uneventful. There was immediate symptomatic improvement.



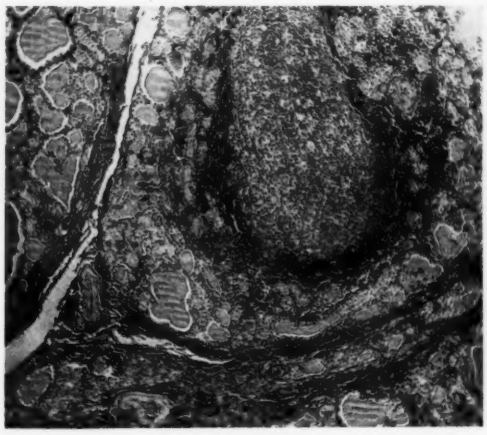


Fig. 1. a, left, Case 1. No. 92994, A. W. Struma lymphomatosa. Marked lymphoid infiltration and hyperplasia with acinar degeneration and increase of fine connective tissue. First operation. b, Second operation, 11 months later. Identical changes compared with those noted at first operation except that the lymphoid tissue is a little more discrete.

At follow-up examination 70 months after operation the patient was completely symptom free. There was still residual induration in the right neck, left neck was normal. There were no signs of myxedema; no dysphagia, or dyspnea; basal metabolic rate was —2 per cent.

Case 9 would certainly be considered by many as a late case of struma fibrosa. Yet her relatively short acute history and the microscopic findings suggest a pseudogiant cell type of chronic thyroiditis. Five years later the right neck, the site of the original involvement, was still hard, indurated, and nontender. This condition is more typical of Riedel's struma. This fact is strong evidence that struma fibrosa is really a late stage of progressive fibrosis of a chronic thyroiditis.

Struma Fibrosa (Giant Cell Variant)

Case 10. No. 192488, C.Z., 43 year old white female housewife, was first admitted to the Strong Memorial Hospital in June, 1942. Her chief complaints were of tender-

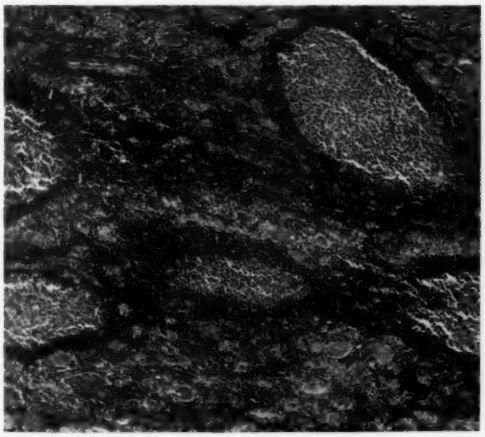


Fig. 2. Case 2. No. 138258, V.K. Struma lymphomatosa. Classical lymphoid infiltration and hyperplasia with acinar degeneration. A minimal amount of connective tissue in this field.

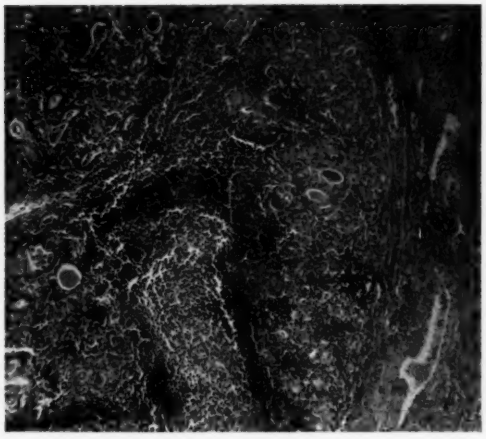


Fig. 3. Case 3. No. 69460, E.A. Struma lymphomatosa. Classical lymphoid infiltration and hyperplasia with acinar degeneration are present with a moderate amount of connective tissue.

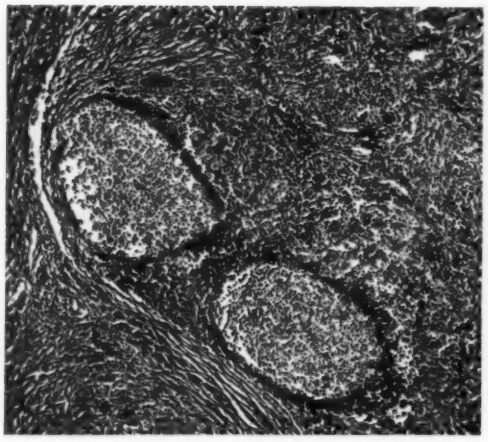


Fig. 4. Case 4. No. 161525, L.S. Struma lymphomatosa. Marked lymphoid infiltration and hyperplasia with acinar degeneration. Marked increase in fibrous connective tissue arranged in whorls. A late case.

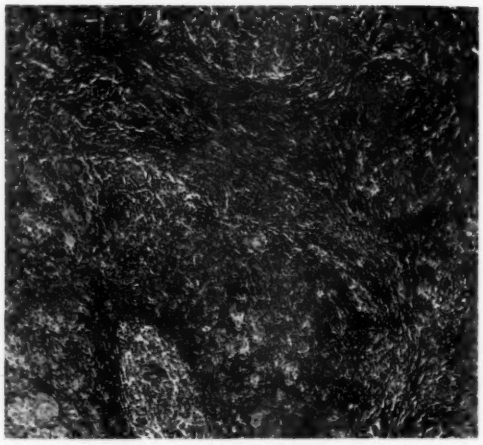


Fig. 5. Case 5. No. 94097, C.S. Struma lymphomatosa. Marked lymphoid infiltration and hyperplasia with acinar degeneration. Marked increase in fibrous connective tissue arranged in whorls. A late case.

ness, sore throat, sharp aching pain of right chest and shoulder, hoarseness, and a moderately productive cough of 3 months' duration. Past history was essentially negative except for many colds and sore throats. She had had 2 normal pregnancies.

Laboratory examination showed a white blood count of 9,300; basal metabolic rate of +17 per cent; Wassermann negative. X-ray revealed a calcified area in right lobe of thyroid. Physical examination revealed a normal temperature, pulse and respirations; blood pressure 120/70. There was a moderate diffuse enlargement of the thyroid which was quite hard. There was a hard discrete nodule in the right lobe.

At operation right subtotal lobectomy was performed. No adhesions were encountered. The left side was moderately enlarged and firm. The tissue excised was yellowish and firm to hard. A calcified adenoma was seen in the specimen. Microscopic examination showed a typical fetal adenoma. The remainder of the sections showed a marked increase in fibrous tissue which in some areas was hyalinized. There were numerous lymphocytes and plasma cells infiltrating the fibrous planes. There were occasional polymorphonuclear cells. The acini were small and compressed. There were frequent pseudogiant cells. In some instances mononuclear cells may be seen infiltrating these cellular aggregates through rents in the acinar epithelium. Postoperative course was uneventful.

At follow-up examination 29 months after operation patient still had pain in the right shoulder that radiates to the right ear. No dysphagia, dyspnea, myxedema, or signs of toxicity were present. Neck was completely soft. Basal metabolic rate was +7 per cent.

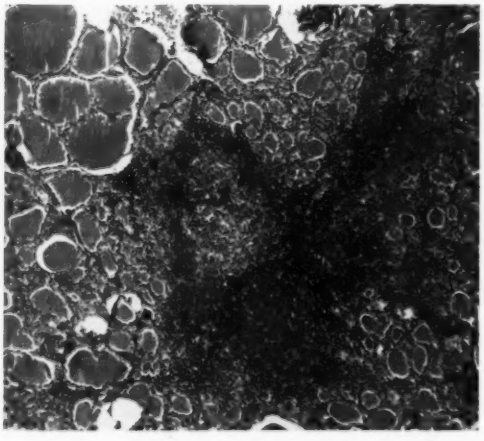


Fig. 6. Case 6. No. 140044, M.W. Struma lymphomatosa. Moderate lymphoid infiltration and hyperplasia. Acinar degeneration in many areas, others present a colloid appearance. Moderate increase in fibrous connective tissue. An early case.

Struma Fibrosa (Giant Cell Variant)

Case 11. No. 161349, I.E., 32 year old white female housewife, was admitted for the third time to the Strong Memorial Hospital in December, 1942. Her chief complaints were of severe headaches, nervousness, enlargement of the thyroid, and tenderness in the left lobe of the thyroid with marked pain on yawning, of 6 weeks' duration. She had been given Lugol's solution by local physician. Past history revealed right otitis media and right mastoidectomy 3 years before admission; tonsillectomy and adenoidectomy 8 years before admission.

Laboratory examination showed a white blood count of 6,000; basal metabolic rate of —11 per cent; negative Wassermann. Physical examination showed a thyroid diffusely enlarged, firm, attached to trachea, and nontender; normal temperature, pulse, and respirations; blood pressure of 130/80.

At operation bilateral subtotal thyroidectomy was performed. No adhesions were noted. Grossly the gland was

beefy in consistency, pale yellowish-gray and quite firm. Microscopic examination showed a marked increase in fibrous tissue, arranged in whorls around acinar epithelium that showed signs of marked degeneration and had coalesced into numerous cellular aggregates very similar to true foreign body cells. There were many of these areas. Mononuclear cells may be seen penetrating these cell masses in some areas. In areas there appear to be true foreign body giant cells. There are many lymphocytes and plasma cells. In areas there are dense accumulations of polymorphonuclear cells forming minute focal abscesses. The picture is that of acute and chronic inflammation. Postoperative course was uneventful. Prompt relief of symptoms was obtained.

At follow-up examination 23 months after operation the patient is essentially symptom free. She has had some gynecological difficulties with the question of pregnancy. Her basal metabolic rate 6 months ago was —8 per cent, at which time she was taking 2 grains of thyroid a day. This was decreased to ½ grain a day and she developed mild symptoms of myxedema and the dosage was again increased to 2 grains a day. At present, 23 months after operation, her basal metabolic rate is —18 per cent. Her neck is soft throughout. She has no symptoms of dysphagia or dyspnea.

Cases 10 and 11 are excellent examples of the pseudogiant cell type of chronic thyroiditis described by De Quervain (13, 14). The latter case is more acute than Case 10. At a casual glance at the microscopic sections, the arrangement of the fibrous tissue of these cases and Cases 4 and 5 seem similar. Yet the two processes are entirely dissimilar in that Cases 10 and 11 are the early stages of an acute to chronic inflammatory process; Cases 4 and 5, the end stage of a chronic degenerative process. The fibrous tissue in struma lymphomatosa is of a finer waving nature than that of struma fibrosa, or its earlier, more acute form in which it is hard, straight, and often hyalinized.

Fig. 7a. Case 7. No. A1236, A.vK. Struma fibrosa. The hard hyalinized character of the fibrous tissue is shown. Thyroid epithelium is relatively normal.

CASE STUDY

The clinical charts and microscopic sections of all the cases, medical and surgical, were reviewed whenever the clinical or pathological diagnoses of acute, subacute, or chronic thyroiditis, fibrosis, lymphoid or cellular infiltration, or granulomatous change of the thyroid were mentioned, stated, or suggested. This study covered a period of 17 years, during which time there were 3,750 admissions for thyroid disease. The protocols and microscopic sections of 8,000 postmortem examinations during this period were also studied in a similar fashion. The cases presented have all been

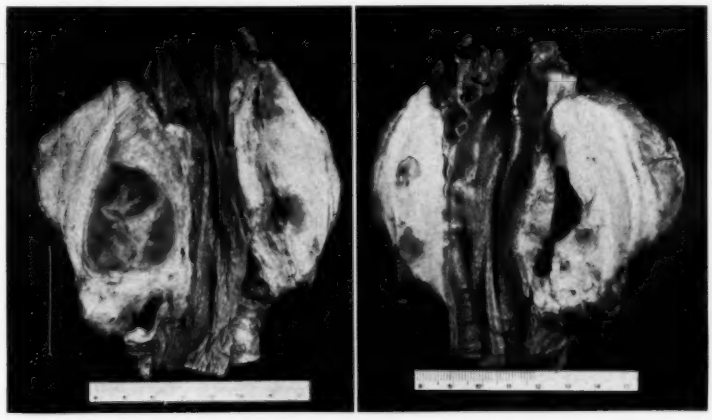


Fig. 7b. Photograph at left shows encirclement of esophagus and compression of an adenoma. Photograph at right shows encirclement of trachea. Both emphasize the hard, white, fibrous, infiltrating character of late cases of struma fibrosa.

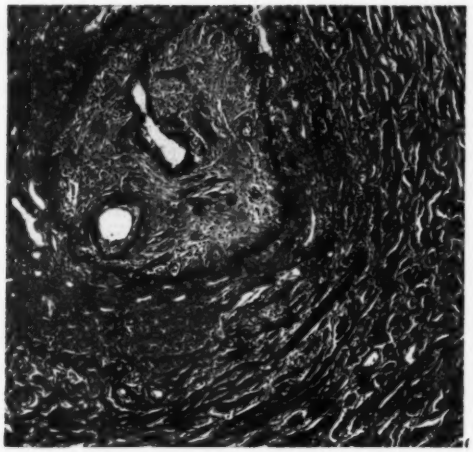


Fig. 8. Case 8. No. 218923, A.K. Struma fibrosa. Marked fibrosis of a hard, hyalinized character. Periarteriolar fibrosis and intimal thickening are shown. A moderate number of leucocytes and lymphocytes in fibrous planes. An occasional pseudogiant cell was noted. Acini fairly normal in appearance.

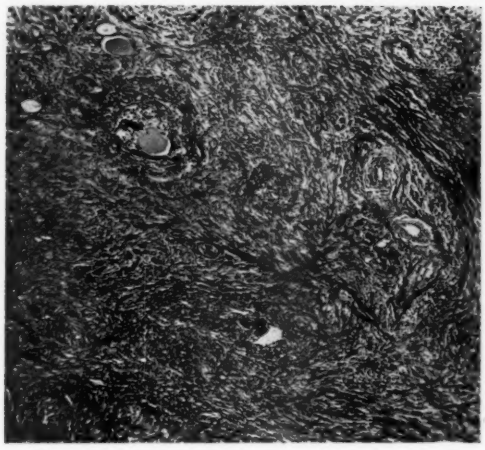


Fig. 9. Case 9. No. 20284, M.V. Struma fibrosa, giant cell variant. Marked increase in fibrous tissue, arranged in whorls, with areas of moderate hyalinization. Moderate numbers of leucocytes and lymphocytes in fibrous planes. Moderate periarteriolar fibrosis. Numerous degenerate acini with epithelium normal elsewhere, in uninvolved areas.

seen personally at recall except 2. In Cases 4 and 7 the patients are dead.

After operation or postmortem examination in many cases diagnoses of chronic thyroiditis or fibrosis of the thyroid were made because of a slight increase in fibrous tissue of the gland or an increase in round cells throughout the stroma. There was no clinical or gross pathological corroboration of these diagnoses. The microscopic pictures were probably representative of the varia-

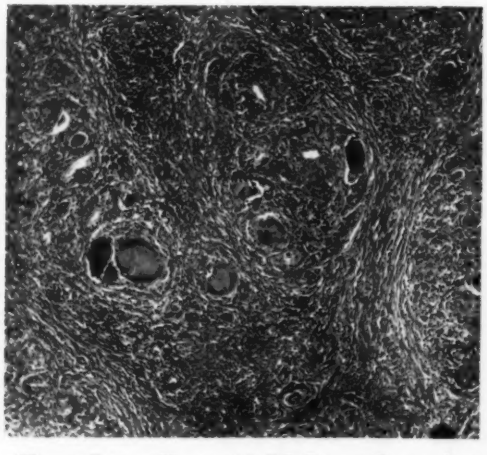


Fig. 10. Case 10. No. 192488, C.Z. Struma fibrosa, giant cell variant. Marked increase in fibrous tissue, arranged in whorls, of moderate hardness and hyalinization. Diffuse and focal infiltrations of leucocytes and lymphocytes. Many degenerate acini with formation of true and pseudogiant cells.

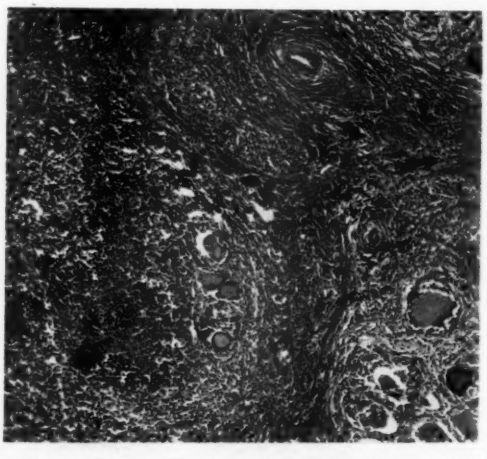


Fig. 11. Case 11. No. 161349, I.E. Struma fibrosa, giant cell variant. Marked increase in fibrous tissue, arranged in whorls of moderate hardness and hyalinization Diffuse infiltration of leucocytes and lymphocytes in fibrous planes. Few focal abscesses. Degenerate acini. Periarteriolar fibrosis and intimal thickening. Numerous pseudogiant cells.

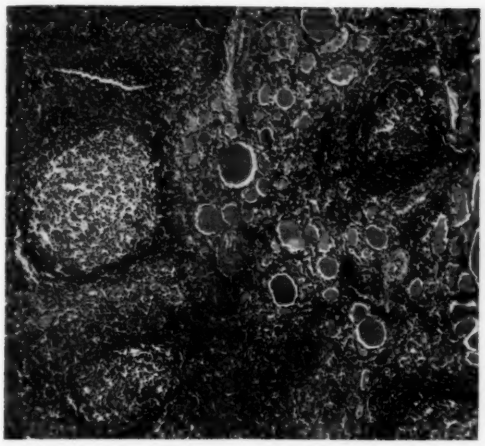


Fig. 12. A6534, A.K. Focal struma lymphomatosa, postmortem. Death caused suddenly at age of 43 by cerebral hemorrhage. No symptoms referrable to thyroid in old record. Microscopic picture indistinguishable from true struma lymphomatosa.

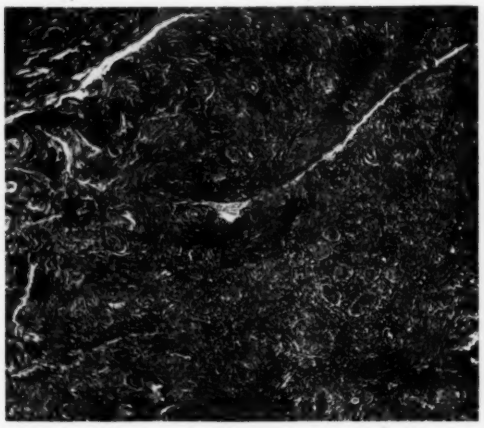


Fig. 13. A373, E.H. True myxedema, postmortem. Marked increase of fibrous tissue of a diffuse finely waving character. Complete acinar degeneration with coalescence into small cell masses. Moderate diffuse lymphoid infiltration without hyperplasia.

tions from normal with increasing age. Attention here should be called to the study of Loeb and Simpson in 1938 on guinea pigs. They noted from birth a gradual increase in fibrous tissue in amount and density. This was most marked about the arterioles and least around the lymphatics of the thyroid. Anterior pituitary hormone stimulation was capable of loosening this stroma.

It is of interest that microscopic sections of the thyroid in 4 cases not reported here showed areas identical with a true struma lymphomatosa. These sections were obtained at postmortem examination for an entirely unrelated disease. These cases are similar to those reported by Jaffe in 1938 and by Simmonds (58) in 1923. They also represent the error that can arise if one judges these cases by microscopic section only.

This small series was selected after reviewing and excluding the following groups of cases: (1) acute, subacute, and chronic thyroiditis of known specific etiology; (2) round cell infiltration and moderate fibrosis of thyroid glands without enlargement, asymptomatic, and usually associated with intercurrent diseases, old age, and debility; (3) focal round cell infiltration, fibrosis, and lymphoid hyperplasia associated with simple colloid goiters, adenomas, or toxic thyroids.

No attempt has been made to distinguish between a strumitis and thyroiditis. The former is inflammation of a pre-existing pathological gland. The latter is inflammation of a normal thyroid gland. Inflammation of the extremes of the normal and pathological can be differentiated easily. In a wide intermediate group, however, it is impossible to say whether inflammation precedes or succeeds pathological change in the thyroid. Thus confusion is avoided in the search for etiological agents or conditions.

Individual features that deserved emphasis in this small series of cases presented are discussed at the end of each protocol.

CLINICAL CHARACTERISTICS

This series is too small to draw any conclusions with regard to a specific clinical summary. However, when they are added to their respective groups reported in the literature they conform to the clinical peculiarities of the disease group in question. In Table I the clinical characteristics of these groups are briefly summarized.

Age. Acute thyroiditis occurs most frequently in young adults. The pseudogiant cell type of chronic thyroiditis and struma fibrosa occur in the third and the fourth decades of life most frequently. Struma lymphomatosa occurs most frequently in the fourth and fifth decades, though there is such a wide range and overlapping that age alone is not a very distinguishing feature in any of the groups.

Sex. Eighty-five per cent of the 3,750 patients admitted to the Strong Memorial Hospital for thyroid disease were females. Thus the ratio of female to male with thyroid disease is roughly 6 to 1. The ratio of female to male in struma fibrosa is stated

TABLE I.—CLINICAL CHARACTERISTICS

	Struma lymphomatosa	Struma fibrosa	Struma fibrosa—giant cell variant
Age—years	40–60	20–40	20–40
Sex—per cent female	Almost 100	60–80	60–80
Predominant symptom	Presence of goiter; vague pressure symptoms	Predominance of pressure symptoms	Moderate pressure symptoms, stabbing shooting pains in shoulder, neck and ear
Duration of symptoms	Usually years, with recent acceleration	1 to 2 years	One to 12 months
Presence of goiter			
Duration of goiter	Usually years	1 to 2 years	1 to 12 months
Degree of thyroid involvement	Always diffuse	30% unilateral	30% unilateral
Response to x-ray	Excellent	None	Unknown
Postoperative	Uneventful	Often stormy	Usually uneventful
Follow-up	Myxedema and general metabolic disorders	No myxedema. Occasionally no relief of pressure symptoms, or surgical complications of tetany or laryngeal paralysis	Usually prompt remission of symptoms, with no recurrence

as roughly 3 to 2 or 4 to 1. In struma lymphomatosa almost 100 per cent of the patients are females. The few exceptions have been noted previously in this paper. Therefore all males with the diagnosis of struma lymphomatosa may be regarded with suspicion unless the entire clinicopathological picture is presented.

Predominant symptoms. Symptoms are varied and often overlap, but in general, the presenting symptom in struma lymphomatosa is diffuse enlargement of the thyroid. Occasionally mild pressure symptoms are noted, such as dyspnea, dysphagia, hoarseness, voice change, tightness about the neck, cough, or stridor. Signs and symptoms of early myxedema may be present. Most common of these symptoms are weight gain, easy fatigability, weakness, dryness of the skin, and mild myxedematous facies. At times tremor, nervousness, insomnia, palpitation, vertigo, and symptoms related to the sympathetic and central nervous system may be present. These are usually secondary to mild pressure symptoms, and are not related to hyperthyroidism which does not exist. At best the complaints of patients with struma lymphomatosa are vague with the one exception that they have a goiter and a fullness of their throat.

With struma fibrosa, this is not true. Pressure symptoms are marked, often to such an extent that asphyxia seems imminent. There are marked secondary nervous symptoms because of the anxiety state created by marked dyspnea and choking sensations. The result of this may be a falsely elevated basal metabolic rate. Pain may or may not be present, but is usually absent. The duration of the symptoms is relatively brief as their severity brings the patient to the doctor and is usually not longer than 1 to 2 years. Case 7 is an exception to this rule.

With the giant cell variant of struma fibrosa, pain is very often the chief complaint and occurs in the neck or shoulder with radiation to the homolateral ear or back of the head. In Case 11 the chief admitting complaint was a severe pain that shot to the back of her head, associated with a diffusely enlarged thyroid. These two symptoms should always lead one to suspect a subacute or chronic thyroiditis. There are often pressure symptoms of mild severity associated with the enlarged gland, but these are variable. Operation is often undertaken within a few weeks of the onset because of the progression of pressure symptoms and the presence of an enlarged lobe or lobes of the thyroid whose hardness suggests malignancy.

Summarizing the complaints presented by these three clinicopathological groups in question, struma lymphomatosa is characterized by a diffuse enlargement usually of long standing with vague associated complaints. Struma fibrosa is marked by a predominance of pressure symptoms with occasional secondary nervous symptoms, and no tendency toward myxedema. The giant cell variant of struma fibrosa is characterized by acute pain in neck or shoulder, radiating to ear or side of the head, and an enlarged, often tender, goiter.

Response to x-ray treatment. Struma lymphomatosa responds readily to x-ray therapy. This is in contrast to the lack of response of struma fibrosa. The response of pseudogiant cell chronic thyroiditis is unknown. X-ray therapy may almost be used as a diagnostic test for struma lymphomatosa, provided that a preliminary biopsy has been taken to rule out malignancy.

TABLE II.—PATHOLOGICAL CHARACTERISTICS

	Struma lymphomatosa	Struma fibrosa	Struma fibrosa—giant cell variant
Gross Surgical appearance	Pseudolobulated, yellowish cast	White, smooth	Gray-white, smooth
Bleeding tendency	Variable	Decreased	Usually decreased
Adjacent adhesions	Pretracheal only	Always present, generalized, very dense	Variable, usually none
Extent involvement	100% diffuse	½ unilateral	½ unilateral
Consistency	Firm	Bone-like	Hard
Presence of adenomas	None	Occasional	Occasional
Microscopic Acinar epithelium	Degenerate, low cuboidal	Compressed, usually absent in involved areas; normal elsewhere	Marked acute degeneration in involved areas; normal elsewhere
Colloid presence	Scanty-absent	Normal in uninvolved areas	Normal in uninvolved areas; intercellular in involved areas
Stroma	Slight to moderate; increase of fine connective tissue	Marked fibrosis with hyalinization	Whorls of fibrous tissue around lobules
Cellular infiltrate	Dense lymphocytic with lymph follicles and germinal centers	Moderate number lymphocytes and leucocytes in fibrous planes	Dense lymphocytic and leucocytic infiltrate plasma cells and histiocytes; many pseudo and true giant foreign body cells
Blood vessels	Uninvolved	Thickening of intima and media	Periarteriolar fibrosis and intimal thickening occasionally

Postoperative course. In general with or without operation cases with struma lymphomatosa tend to become myxedematous and must be supported by thyroid extract. Struma fibrosa and its giant cell variant seldom cause myxedema provided that enough normal thyroid tissue has been allowed to remain after thyroidectomy. However, in struma fibrosa, pressure symptoms are apt to progress, and there is often a residual hardness and induration toward the periphery of the lobes where resection was incomplete, and as such these two groups are indistinguishable months or years after operation. The giant cell variant of struma fibrosa may subside spontaneously if left alone, though its symptoms may be so annoying that operation cannot be withheld. In conclusion, the fact that very few of the cases of any of these groups have had second operations, is ample evidence that they become stationary with regard to their mechanical effects. Moreover, these effects can usually be alleviated by one operation. Struma lymphomatosa does progress physiologically however, as has been noted.

Laboratory. Laboratory examination offers little diagnostic aid, with the exception of the basal metabolic rate which as noted is usually normal or slightly elevated in struma fibrosa and its giant cell variant, and low in struma lymphomatosa. If the basal metabolic rate is quite low the blood cholesterol may be elevated. Anemia is not a constant feature unless there is marked myxedema. McSwain and Moore state that there is a relative lymphocytosis in the blood smear in some cases of struma lymphomatosa without elevation of the the white blood cell count. The Wassermann and tuberculin tests are no different than would be expected in any group of people and are not a constant feature in their results. Cultures and bacterial smears of the thyroid have been constantly negative.

Pathology. In considering the pathology of these groups one should correlate the findings at physical examination, the gross surgical pathology, and the microscopic report.

Physical examination. In struma lymphomatosa the gland is diffusely firm; occasionally it is described as hard. The largest gland, described by McSwain, was 177 grams. Often it is fixed to the trachea on swallowing. The gland is seldom tender. It may be asymmetrical in its enlargement, but as Joll states, the normal thyroid is often asymmetrical in its development and occasionally a whole lobe is lacking. This fact can explain the asymmetrical enlargements of Case 1 and the markedly enlarged isthmus that was removed in Case 4. In struma fibrosa and the giant cell form of chronic thyroiditis, diffuse enlargement occurs in about 70 per cent of the cases. It is localized in one or more lobes in the remainder. If the examination is carried out with care, fixation to the tissues is almost always noted. The gland is intensely hard. Tenderness is a fairly constant feature in the chronic thyroiditis. In none of these forms is a bruit heard. Nodules are very rarely felt and in 1 case in which they were described preoperatively they were absent on surgical exposure.

This is an important differential point from a malignant lesion. Regional lymph nodes are seldom enlarged.

Gross pathology. The gross appearance of the gland corroborates a careful physical examination with regard to size, shape, and consistency of the gland. In struma lymphomatosa the diffuse enlargement may proceed posteriorly in such fashion as completely to encircle the trachea. The diffuse involvement includes all prolongations and extensions of the gland. The surface of the gland is smooth, pinkish in color, with a pseudolobular or bosselated appearance. The cut surface appears finely lobular with a yellowish cast that is characteristic. There are no adjacent adhesions except a thickening in some instances of the normally existing pretracheal attachment. The gland is firm in consistency at operative exposure though it may feel hard to preoperative examination. The amount of bleeding is variable at operation.

In struma fibrosa the gross appearance is characteristic. The gland is white, glistening, smoothly enlarged, extremely hard, avascular except where fibrous tissue maintains the patulousness of a large vessel, and densely adherent to surrounding soft tissue and pretracheal muscles. The gland cuts with difficulty and resection is often physically impossible except by continual sharp dissection without identity of adjacent structures, nerves, or vessels. As in Case 7 the esophagus may be completely surrounded. In no case of true struma fibrosa is this adhesive characteristic lacking unless a lobe is uninvolved. In 30 per cent of the cases the process is localized to one or two lobes of the thyroid. Frequently this fibrous enlargement of a lobe will encapsulate and compress a colloid adenoma, as was true in Case 7.

The gross pathology of a pseudogiant cell thyroiditis is very similar to a struma fibrosa in size, shape, consistency, and extent of involvement except that this form lacks adhesions to the surrounding soft tissues, and if present they are less dense. Very frequently, however, a perithyroiditis is described in operative notes in which a thickening of the capsule and an induration of surrounding tissues are noted. This picture has been given particular emphasis by De Courcy (11, 12) and will be discussed later under etiology.

Microscopic findings. In this description, the state and appearance of the acinar epithelium, the presence or absence of colloid, the appearance and degree of fibrosis in the stroma of the gland, the character of infiltrating cells, and the status of the blood vessels, warrant careful consideration.

Struma lymphomatosa presents a diffuse and uniform degeneration of the acini, as is evidenced by a flattening of the epithelium to a very low cuboidal type with eccentrically placed dark nuclei. The acini shrink in size and become smaller. They have a tendency to coalesce with the formation of pale, degenerate cells. Colloid is scanty or absent. Rarely does one see a pseudogiant cell, formed by an admixture of remaining colloid and acinar epithelial cells. Occasionally, depending on the level of the section with regard to any one thyroid vesicle, one sees an intra-acinar cell mass of desquamated epithelial cells and colloid if such is present. One sees constantly an increase in fibrous connective tissue surrounding the lobules of degnerating acini. This increases in amount as the disease process continues. Often in the late stages one may see complete fibrous replacement of whole lobules. However, this fibrous tissue is of a finer waving texture that serves to distinguish it from the hard, coarse type found in struma fibrosa. The arrangement of this fibrous tissue assumes characteristic finely waving whorls about the lobules in the late states of this disease, and is often confused with the early appearance of the fibrous tissue in the giant cell variant of struma fibrosa. Here, however, as in struma fibrosa, the fibrous tissue is hard and coarse. Undoubtedly, this apparent similarity has been the cause for many writers to consider the two as one disease process. There is a diffuse infiltration of lymphocytes throughout the gland, in all cellular planes, and between the acini. There are numerous areas of lymph follicles with their characteristic germinal centers composed of larger lymphocytes and reticulum cells with their mitotic figures. Plasma cells are occasionally seen. Leucocytes are rare and found with difficulty, if at all. Large monocytes are occasionally seen and rarely one sees a pseudogiant cell which has been described. There is no endarteritis or thickening of the media of arterioles in struma lymphomatosa, and there is no undue vascularity of the gland.

Struma fibrosa presents a striking picture of hard, dense, hyalinized, straight, fibrous tissue and little else at a casual glance. On further inspection one may note compression of epithelial elements if they remain. In the involved areas, however, there is usually complete absence of acinar epithelium. When present in the uninvolved areas the acini appear fairly normal with varying sizes, shapes, and colloid content. The epithelium is usually normal cuboid type with centrally placed nuclei. There are usually numerous chronic and acute inflammatory cells that have infiltrated the connective tissue planes. Their amount depends on the area looked at and the stage of the process. In the late stages of struma

fibrosa, these infiltrating cells are less frequent. Scattered lymphocytes are most frequent. There are no germinal centers or areas of hyperplasia. Occasional leucocytes are seen. Plasma cells and wandering monocytes are seen in varying numbers. Occasionally, pseudogiant cells are seen though even these are very rare or absent in the late stage, which in brief shows little else but fibrosis. The arterioles show a thickening of the intima and media and the vessels are surrounded by a cuff of fibrosis in most instances.

The giant cell variant of struma fibrosa presents a much wilder picture microscopically. There is an acute degenerative process in the acinar epithelium and often in one low power field, many stages of this degeneration may be seen. Acini appear normal in uninvolved areas. These stages of degeneration vary from only hyperchromatic nuclei to a coalescence of epithelial cells with the formation of an intra-acinar cell mass or a pseudogiant cell. As the acinar epithelium degenerates, the continuity of the wall of the vesicle becomes lost. First it thins in one area, then proceeds to a more complete breaking up. Colloid is often left in open tissue spaces. In some areas large monocytes may be seen penetrating these cellular aggregates. In other areas, where no colloid is present, and no acinar epithelium can be distinguished, these pseudogiant cells are indistinguishable from true foreign body cells of the Langhans type. In fact, ultimately these cellular aggregates, that include acinar epithelium, monocytes, and colloid, may be true foreign body cells. This could result from absorption of the colloid and degenerate epithelial cells by the accompanying monocytes. This conclusion is borne out by the fact that in the late stages these giant cells have fewer nuclei than the earlier aggregates of cells. There is a marked increase in fibrous tissue that is hard, coarse, and often hyalinized, though to a lesser degree than in struma fibrosa. It is arranged in characteristic lobular whorls and is to be distinguished from the late fibrosis of struma lymphomatosa, as mentioned.

Interspersed are numerous lymphocytes and plasma cells. Occasional eosinophils can be seen. In areas numerous leucocytes are present, and focal necrosis is suggested. No bacteria, spores, or micro-organisms of any sort are seen that might implicate some specific etiology.

The small arteries and precapillary arterioles uniformly show thickening of the intima and media, particularly if a silver tissue stain is used. This fact is very beautifully demonstrated by German, using the Hortega, silver-gold impregnation technique. It is also emphasized by De Courcy (11, 12).

Thus in these three clinicopathological groups, irrespective of their relationships, certain pathological characteristics are present. In struma lymphomatosa, diffuse enlargement of the thyroid with dense lymphocytic infiltration and hyperplasia associated with degenerate acini may be seen. In struma fibrosa there are the dense perithyroid adhesions and diffuse fibrosis. In the giant cell variant of struma fibrosa one notes particularly the presence of cellular aggregates resembling foreign body giant cells with acute degeneration of the acini, giving the gland a granulomatous appearance.

Pathogenesis and etiology. Little has been concluded about the relationship and etiology of these diseases. With regard to the relationship of struma lymphomatosa and struma fibrosa, there are three trends of thought. First, they are the early and late manifestations of the same disease process, (Ewing, Heyd, Coller). Second, they are different manifestations of the same process, (Eisen, 17; Womack). Third, they are separate and distinct pathological groups (Hashimoto, 30; Graham, 25, 26, 27; McClintock and Wright; Clute *et al.*; Harry; Lee; Joll; Hellwig; McSwain and Moore). Throughout this paper emphasis has been placed on the latter view so that a restatement of their differences is unwarranted. Yet to consider the two entities, one must have a concept of different etiologies.

Therefore, the relationship of the so called pseudogiant cell thyroiditis to struma fibrosa is worthy of further attention. This brings up the entire subject of bacterial thyroiditis and toxic thyroiditis. It seems logical to conclude that the distinctions made in these groups are not justified.

When one considers the anatomical location of the thyroid, its rich blood supply, its proximity to the throat and nasal passages, it undoubtedly becomes contaminated frequently with bacteria of the flora of the mouth and nose, and by bacteria from distant points with infections. The rich blood supply of the thyroid in general prevents bacteria from propagating. Thus the presence of an abscess on the one hand with a specific organism isolated and an acute nonsuppurative thyroiditis on the other are in a large measure the result of the balance of the virulence of the organism and the resistance of the host. Usually, because of the rich blood supply, focal or large abscesses seldom develop. Thus, as Crotti stated, a bacterial, nonsuppurative thyroiditis is only a phase of a process whose last act is suppuration, and there is no way of telling beforehand which way a given process will turn. If there is a pre-existing area of disease, as a colloid adenoma, this would ob-

viously be a *locus minoris resistantiae*, and such a gland would be more susceptible to an inflammation of the suppurative or nonsuppurative variety. Numerous organisms have actually been identified in specific suppurative thyroiditis, including the streptococcus, the staphylococcus, Bacillus coli, Bacillus typhosis, and the pneumococcus. This supports the fact that the thyroid is often inoculated bacterially. It is well known that the blood stream will sterilize itself with surprising alacrity after showers of bacteria of different type by injection or from septic foci. Often the only clinical manifestation will be a chill and fever. Therefore, in the thyroid these same conditions exist. After contamination with bacteria via the blood stream or lymphatics, the thyroid becomes sterile because of its rich blood supply. Only the local toxic effects of the bacteria or their exotoxins on the acinar epithelium remain. This condition results in the socalled toxic nonspecific thyroiditis which may be of a mild or severe nature, and may regress with few clinical symptoms or may progress. With marked acinar destruction and release of colloid, a second group of irritating substances are freed in the intercellular spaces, namely thyroglobulin and degenerate, nonviable epithelium. These substances must be resorbed. Whether a proteolytic enzyme in the colloid exists, whether it is activated if existent, and whether it exerts an inflammatory effect if existent, remains a question. Recent research suggests the presence of such an enzyme. This secondary process of repair and resorption is long and may or may not be attended with fever and toxic clinical symptoms. The end-result is replacement fibrosis of the locally damaged areas. As De Courcy (11, 12) has emphasized, there is often a local perithyroiditis noted at the time of operation which he believes creates a periarteriolar fibrosis, with thickening of the arterial intima and media. This condition may produce a compensatory fibrosis of the thyroid gland. He has compared this with Goldblatt's description of a compensatory fibrosis of the kidney after constriction of the renal blood supply. Thus in addition to a replacement fibrosis of damaged lobules, there may be a secondary compensatory fibrosis of the gland of a progressive nature.

Inflammation of the thyroid by a specific filterable virus is a possibility but there is no evidence for or against such an agent at present.

This concept of the inflammatory origin of struma fibrosa and its giant cell variant is borne out experimentally. Chemical poisons, such as phosphorous and silver nitrate, cause a toxic thyroiditis with a histologic picture of acinar degeneration, desquamation of epithelial cells, scanty colloid, and chronic and acute cellular infiltration. De Quervain found that the introduction of bacterial toxins into the general and thyroid circulation had similar effects. De Quervain noted that the injection of a pure culture of bacteria into the artery of the thyroid could pass through without effects or might cause the disappearance of colloid, desquamation of the epithelium, and leucocytic infiltration.

Further, there is a relation of the thyroid to infectious diseases in man. Sokoloff and Muller independently in 1896 first showed that in acute infectious diseases fatty degeneration of the acinar epithelium occurred with desquamation. Roger and Garnier in 1900, examining the glands of people dying from acute infectious diseases came to similar conclusions, as in almost every case marked microscopic changes occurred of a proliferative or a degenerative nature or both. In patients dying of tuberculosis a more dense sclerosis was noted leading to the conclusion that the denser fibrosis was due to tuberculous toxins. Similar results were reached later by De Quervain. Sarbach concluded, after investigation of 67 cases, that "acute infections may produce thyroid histological alterations with increase in size and number of alveolar cells, their degeneration and desquamation, liquefaction, diminution of the colloid, and hyperemia. The connective tissue remains intact." Esmonet found in cachectic conditions such as carcinomatosis, tuberculosis, and leucemia, that epithelial elements underwent a fatty degeneration. Gregor, reporting on 26 thyroids examined from children dying of scarlet fever, found similar changes to those noted.

Thus in addition to a direct local effect of bacterial toxins and bacteria on the thyroid, there is a response of the thyroid often in a degenerative form to systemic diseases. This response is to be expected because of the thyroid's rôle in the regulating of metabolism which is altered by these diseases. Those who feel that struma lymphomatosa and struma fibrosa are different manifestations of the same process may cite this as evidence, in that struma fibrosa may be the result of the direct infection of the thyroid gland and that struma lymphomatosa represents the degenerative response or burning out of the thyroid because of its response to systemic disease. Perhaps this may rarely occur and may be the explanation of the etiology in Case 4, a male, but if so, the incidence of males to females should almost be equal in struma lymphomatosa.

The etiology of struma lymphomatosa is more obscure. As Joll concluded, struma lymphomatosa

appeared to be "neither inflammatory, neoplastic, nor degenerative in any way comparable with what is usually understood pathologically by such terms." The stimulus for the characteristic picture of diffuse lymphoid infiltration is difficult to account for. In fact, the function of lymphoid tissue in general remains a mystery. Maximow states that the lymphoid tissue responds to local injury, is related to the extramedullary formation of lymphocytes, and is related to the formation and function of macrophages.[1] Lymphoid tissue is rarely seen in normal thyroids of young adults, but is more frequently witnessed in apparently normal thyroid glands of older adults over the age of fifty (Simmonds, 57). It may be a response to a local degenerative process.

The fact that struma lymphomatosa occurs almost entirely in women in the fifth and sixth decades of life with an associated progressive tendency to myxedema seems to indicate a degenerative process in contrast to a neoplastic or inflammatory process. The thyroid is subject to excessive functional demands in women throughout their period of sexual activity, namely, puberty, menstrual cycles, pregnancies, and the menopause. It seems logical to conclude that through the years the gland burns itself out, and the lymphoid infiltration and hyperplasia is a compensatory and replacement process for the slowly degenerating acini. The rather rapid hyperplasia locally of the lymphoid tissue often suggests great intrinsic, almost neoplastic activity, though not sufficient to relate it to any form of malignant degeneration, as mentioned by Graham (26). Whether this degenerative process is preceded by an initial hyperplasia and toxic reaction remains a question. Some contend that this always occurs, and thus they explain the focal areas of lymphoid tissue in a toxic goiter.

Boyden, Coller, and Bugher are of the opinion that iodine ingestion is a possible factor. However, in many cases no history of iodine ingestion is present. Furthermore, few patients have thyroid disease of any sort, who do not get iodine, rightly or wrongly, at some time or other in the course of their disease. The frequency of its administration, particularly in struma lymphomatosa, is evidence of its chronicity and cannot be considered justly as an etiological agent.

Diet has been considered. McCarrison produced a lymphadenoid goiter in 25 per cent of his rats on a vitamin deficient diet. He fed potassium iodide salt. He suggested that a vitamin deficient diet was a possible etiology in man for struma lymphomatosa. His work is very interesting and may be significant, though in many cases no history of dietary insufficiency is to be found.

One interesting discussion of etiology is that of Hellwig. He felt that overstimulation of the thyroid by the pituitary thyrotropic hormone was responsible for its involution and degenerative changes. He aptly makes the comparison of the microscopic appearance of struma lymphomatosa to chronic cystic disease of the breasts. The work of Uhlenhuth in 1926, showing that the colloid release phase is affected by the thyrotropic hormone, is emphasized by Hellwig. This work has been carried a step further by the experiments and microdissection of the thyroid follicles of rats by De Robertis in 1941 and by Dziemian in 1943 at Johns Hopkins. They found that the proteolytic enzyme factor in colloid was affected by the thyrotropic hormone. Administration of thyrotropic hormone caused a decrease in the viscosity of the colloid, thus facilitating its release.

The end-result of a rather large amount of speculation and very little actual research is essentially that the etiology of struma lymphomatosa is unknown. Because of this one cannot state with definitiveness its precise relationship with any of the existing known diseases of the thyroid gland. Thus one must continue to regard struma lymphomatosa as a clinicopathological entity of unknown etiology, and not, for the present at least, a specific disease. Struma fibrosa, on the other hand, seems quite definitely, from the cases studied and from reports in the literature, to be the result of an inflammation of the thyroid of a bacterial origin. The pseudogiant cell type of thyroiditis described by De Quervain does not seem to be a disease, *sui generis*, as he maintains, but one variant of the protean manifestations of the thyroid gland to inflammation of bacterial origin.

DIFFERENTIAL DIAGNOSIS

Obviously, the most important differential diagnosis for these groups is from malignant growths. Due to their infrequent occurrence, one's first acquaintance with the disease is often at the operating table. The question of malignant growth has either been raised clinically preoperatively, or imposes itself on exposure of a firm or hard gland. In mistaken diagnosis of malignancy, the surgical error is usually one of commission, and not omission. There is an attempt made at total excision of the thyroid with often unilateral or bilateral damage to the recurrent

[1]Recent research has suggested that lymphocytes are a storehouse of antibody protein and that they may be the site of antibody production. Further, the rate of liberation of antibody from lymphoid tissue is under the control of pituitary-adrenal cortical secretion. This may indicate a relationship to bacterial or nonspecific inflammation and may be correlated with Hellwig's concepts. Dougherty, T. F., Chase, J. H., and White, A. Proc. Soc. Exp. Biol., N. Y., 1944, 57: 295–298.

laryngeal nerves, parathyroid tetany, myxedema, or varying combinations of these complications. One case is known in which all these complications occurred postoperatively. Complete resection of a struma fibrosa is usually mechanically impossible. Complete resection of a struma lymphomatosa is technically easy but unnecessary and actually very undesirable from a physiological point of view. Therefore, to endanger the patient's well-being and even life by a total resection of the gland is not justified, except on a definitely positive diagnosis of malignant lesion, supported by microscopic section.

The differential features are easy to describe but often difficult to apply when there is a specific case in question. In general, cancer occurs in 1 to 2 per cent of all thyroidectomies. It is rare for a cancer to occur in a previously normal gland. Cancer usually occurs between the ages of 40 and 60 with wide variations, however, and with twice the frequency in females. Usually the malignant tumor is nodular with an irregular surface contrasted to the diffuse smooth enlargement in these groups of cases. There is frequent invasion of adjacent tissues with regional lymph node involvement. This condition may be quite difficult to distinguish from a late hard struma fibrosa. However, the diffuseness of the later process, even if confined to one lobe, and its excessive hardness, serve to differentiate it from a malignant tumor. If there is any doubt, on review of the clinical history, gross pathology, or even frozen section, it is advisable to wait for permanently stained microscopic sections.

TREATMENT

Treatment should be aimed at relief of symptoms. A positive diagnosis is essential. Thus biopsy, irrespective of the form of treatment, should be carried out as a preliminary procedure if there is any question of the diagnosis at operation, or if treatment solely by x-ray is contemplated.

In general the best results are obtained by the most conservative means. The use of x-ray only, following biopsy, has given excellent results in struma lymphomatosa. It may almost be used as a diagnostic test. The response is rapid and the gland will shrink markedly in size in 2 or 3 weeks. A radium collar has been described by Renton and associates. Deep x-ray of high enough voltage is sufficient up to 1200 to 1500 r on each side of the neck in divided doses of 100 to 200 r. Time must be allowed to elapse between courses of radiation to allow for skin tolerance of the amount of radiation given. In Case 4 the patient had a permanent regression of his gland after 800 r to each side of his neck anteriorly. In Case 6 the patient had an immediate response to the same amount, 800 r, within 2 weeks, but she had a recurrence of the size of her thyroid after 6 weeks. She received another course of 600 r with excellent results.

The effect of x-ray therapy on pseudogiant cell thyroiditis may be sufficient to warrant its use. However, it is hard to evaluate as this earlier, more acute form of thyroiditis often subsides spontaneously and without operation. X-ray therapy is ineffective for the late stages of fibroses described under struma fibrosa.

Surgical treatment is carried out for one reason: the relief of the mechanical effects of the enlarged or fibrous gland. In struma lymphomatosa the patient is usually in a hypothyroid state. Therefore, the less subnormal tissue removed the better, for functional reasons, provided that sufficient tissue is removed to relieve mechanical symptoms. Furthermore, struma lymphomatosa may have a tendency to regress, after a number of months. Case 3 is an example in which the maintainence dose of thyroid is now much less than immediately after operation. In far advanced struma fibrosa, removal of a strip or wedge of tissue overlying the trachea is all that can be physically accomplished in many cases without undue danger to the patient. The amount of tissue excised of course depends on the findings with each patient. With pseudogiant cell form of chronic thyroiditis, with fewer perithyroid adhesions, subtotal excision of a lobe or lobes, or the removal of a wedge of tissue over the trachea is much easier. One should remember, however, that normal tissue need not be excised and that the disease usually spontaneously regresses. Therefore, excision of involved tissue in all cases should be as conservative as possible.

With regard to the actual technique of surgery little need be said. The potential complications have been mentioned. Because of the greater mechanical difficulties in surgery on thyroid glands with marked fibrosis and adhesions to surrounding soft tissues, the frequency of these complications is greater. For this reason one must use extreme care, particularly with regard to the recurrent laryngeal nerves. Damage to these nerves is undoubtedly the cause for frequent tracheotomies in many of the earlier cases reported and not because of a progression of the disease. The entire purpose of the operation—to relieve obstruction to an airway—is defeated when one or both of these nerves are cut. Acute asphyxia may occur when paralyzed vocal cords are added to an already embarrassed airway. Therefore,

for the postoperative safety of the patient, the vocal cords should be inspected upon conclusion of the operative procedure as well as between stages of the operation when it is in progress. Tracheotomy may thus be anticipated and actually performed if necessary, thus reducing the risk of asphyxia to the patient. The use of an intratracheal tube for administration of anesthesia may be a necessity for an adequate airway if general anesthesia is used.

The results of surgery in general are good. This is borne out by the fact that so few cases have had second operations. The patients with struma lymphomatosa almost invariably need supportive thyroid extract irrespective of the amount of the gland excised, though less thyroid extract will be necessary if more thyroid tissue is allowed to remain. In the more acute forms of thyroiditis without marked fibrosis, relief of symptoms is usually quite prompt and permanent. As one might expect, the results of surgery in a late struma fibrosa are often poor. The poorer end-results are primarily because of the nature of the pathology, and secondarily because of postoperative surgical complications of recurrent laryngeal nerve paralysis, parathyroid tetany, and occasionally myxedema.

SUMMARY CONCLUSIONS

Riedel first described a diffuse fibrosis of the thyroid in 1896. In 1904 De Quervain first described a giant cell type of thyroiditis. In 1912 Hashimoto described a diffuse struma lymphomatosa. Since these original descriptions there has been much confusion of case reports, though at present struma lymphomatosa is considered by most a clinicopathologic entity, despite the weight of Ewing's opinion to the contrary. Struma fibrosa and its giant cell variant have been confused in the literature and no attempts have been made to present their relationships.

Eleven cases are presented with clinical and pathological evidence to support their diagnosis. Six cases were diagnosed struma lymphomatosa; 2 cases were diagnosed struma fibrosa, and 3 cases represent the earlier, more acute, giant cell variant of struma fibrosa.

The three small groups of cases are discussed separately to emphasize their relationships, similarities, and dissimilarities. Their clinical and pathological characteristics are summarized in Tables I and II.

Struma lymphomatosa is considered a distinct clinicopathologic entity. Its etiology is unknown, though it is considered a degenerative disease in contradistinction to a neoplastic or inflammatory disease. The excessive demands on the thyroid during the sexual life of the female are considered fundamental in the etiology of this disease. These excessive demands may be mediated through the hypophysis.

Struma fibrosa and its giant cell variant are considered two late manifestations of the thyroid from an acute to chronic inflammatory process. The fibrosis of the gland is considered first a replacement phenomenon of damaged glandular tissue. In later stages the diffuse infiltrating type of fibrosis may be due to a compensatory mechanism through constriction of the arteriolar blood supply of the gland, from a coincidental perithyroiditis.

The pseudogiant cells are merely evidence of the more acute nature of the inflammatory process which may regress or more rarely progress to a diffuse infiltrating fibrosis.

Emphasis is placed on the protean manifestations of the thyroid gland to inflammations resulting from bacteria, systemic disease, and poisons. By nature of its rich blood supply, suppuration is rare. The rôle of a virus as an inflammatory agent is yet undetermined.

The important differential diagnosis is from malignant growth.

Treatment of struma lymphomatosa by radiotherapy is the method of choice after a preliminary biopsy.

Surgery of struma fibrosa should be as conservative as possible. Its purpose is the relief of mechanical effects only as this disease is not neoplastic. Radiotherapy may be effective in the earlier, more acute, giant cell variant of struma fibrosa. The risk of operative complications of parathyroid tetany and recurrent laryngeal nerve paralysis is markedly increased in any radical attempt at extirpation of the gland and nullifies any potential relief of preoperative mechanical obstructive symptoms to the airway of the patient.

The end-result of treatment, barring surgical complications, is usually good, though with struma lymphomatosa there is a progressive tendency to myxedema.

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TABLE I.—SUMMARY OF THIRTY-EIGHT CASES*

Case, Sex	Age, years	Treatment	Survival at last report	Bronchus involved
1 M	18	Pneumonectomy	4 mos.	Right upper lobe
2 M	22	Pneumonectomy	†	Right main
3 F	43	Pneumonectomy	7 mos.	Left upper lobe
4 F	42	Pneumonectomy	4 yrs.	Left main
5 F	42	Pneumonectomy	†	Left upper lobe
6 M	33	Pneumonectomy	1 yr.	Left lower lobe
7‡ M	15	Pneumonectomy	Died	Right upper lobe, right main
8 M	31	Pneumonectomy	1 yr.	Right upper lobe
9 F	42	Lobectomy	†	Right lower lobe
10 F	25	Pneumonectomy	†	Left lower lobe
11‡ F	47	Diathermy and x-ray	Died	Right main
12 F	61	Lobectomy	6 mos.	Middle lobe
13 F	41	Lobectomy	8 mos.	Right lower lobe
14 M	42	Lobectomy	7 mos.	Left lower lobe
15 M	19	Lobectomy	3 mos.	Middle lobe
16 M	25	Diathermy and x-ray	5 yrs.	Right lower lobe
17 M	59	Diathermy, radium, x-ray	4 yrs.	Right lower lobe
18 M	49	Diathermy, radium, x-ray	8 yrs.	Right main
19 M	48	Diathermy, radium, x-ray	4½ yrs.	Left lower lobe
20 M	55	Diathermy, radium, x-ray	Died	Left lower lobe
21 F	23	Diathermy and x-ray	7 yrs.	Left lower lobe
22 F	59	Diathermy, radium, x-ray	2 yrs.	Left upper lobe
23 F	40	Diathermy, radium, x-ray (exploration)	9 mos.	Left lower lobe
24 F	38	Diathermy and x-ray	26 mos.	Left main
25 M	23	Diathermy and radium	1 yr.	Right lower lobe
26 M	41	No treatment	1 yr.	Right main
27 M	40	No treatment	Unknown	Right lower lobe
28 F	41	X-ray	4 yrs.	Right lower lobe
29 F	31	Diathermy and radium	3 yrs.	Right lower lobe
30 F	63	Diathermy and radium	1 yr.	Right lower lobe
31 F	44	Diathermy and radium	2 yrs.	Right main
32 F	26	Diathermy and radium	2 yrs.	Right main
33 F	24	Diathermy and radium	8 mos.	Left main
34 F	30	X-ray	12 yrs.	Right lower lobe
35 F	25	X-ray	6 yrs.	Right lower lobe
36 M	37	Diathermy	3 mos.	Left upper lobe
37 F	20	Diathermy	2 mos.	Right lower lobe
38 F	41	Diathermy	Under treatment	Left upper lobe

*The first 15 cases in this table are the same as those in Table II. They are listed in the same order.
†Alive shortly after operation; no report since. ‡Necropsy.

TABLE II.—ADENOMA OF LUNG: PATHOLOGIC FINDINGS IN CASES IN WHICH LUNG WAS AVAILABLE FOR STUDY

Case	Size of tumor, cm.	Peribronchial extension	Condition of lung distal to site of tumor
1	1.4	Yes	Moderate pneumonitis. Mild bronchiectasis
2	0.8	No	Moderate bronchiectasis of all bronchi. Moderate pneumonitis
3	3 by 2.5 by 0.9	Yes	Mild pneumonitis. Little bronchiectasis
4	1	Yes	Mild bronchiectasis and pneumonitis
5	3.5	Yes	Marked bronchiectasis. Mild pneumonitis
6	1.5	Yes	Mild bronchiectasis and pneumonitis
7*†	2.5 by 2 by 1.4	Yes	Marked bronchiectasis and pneumonitis
8	0.7	Yes	Marked bronchiectasis and pneumonitis
9	2	No	Moderate bronchiectasis and pneumonitis
10	8.5 by 6 by 5	Yes	Marked bronchiectasis and pneumonitis
11†	1	Yes	Marked bronchiectasis and pneumonitis
12	4	Yes	Practically no bronchiectasis or pneumonitis
13	3.5 by 2.3 by 2.2	Yes	Marked bronchiectasis and pneumonitis
14	3.2	Yes	Practically no bronchiectasis or pneumonitis
15	3.6 by 2.6 by 2.5	Yes	Marked bronchiectasis and pneumonitis

*Lymph node infiltrated with neoplasm. †Necropsy.

and often recurrent attacks of pneumonia in the same lobe was frequently noted. In 46 per cent of our cases there was a history of one or more attacks of acute pulmonary infection, and in many instances the first evidence of an endobronchial lesion was an acute febrile episode usually diagnosed as pneumonia.

Another important symptom caused by the bronchial obstruction is the so called asthmatoid wheeze, which may vary from slight wheezing respiration to rather marked asthma or even severe stridor. Since these tumors fairly frequently have long pedicles, the attacks of asthma may be precipitated by change of position and often are paroxysmal. Wheezing was a prominent symptom in 23 per cent of our cases and was the initial symptom of which the patient complained in 14 per cent.

If the bronchial obstruction is allowed to persist without treatment, pulmonary suppuration ultimately develops in the distal portions of the affected lung. This may take the form of bronchiectasis, pulmonary abscess, pulmonary gangrene, or empyema. In 23 per cent of our cases there

was clinical evidence of pulmonary suppuration. These secondary processes sometimes become so marked that they fairly frequently obscure or even obliterate the primary lesion. In fact, pulmonary suppuration, rather than the tumor *per se*, is the chief cause of death in most cases.

Since the signs elicited by physical examination are usually dependent on the degree of bronchostenosis and the amount of pulmonary suppuration, they may vary considerably. Over the affected region there are usually decreased expansion of the thorax, impaired resonance and decrease of breath sounds.

ROENTGENOGRAPHIC EXAMINATION

Direct or indirect evidence of an endobronchial lesion may be obtained by roentgenographic examination of the thorax. The tumor mass can at times be clearly outlined by tomographic studies and at times can be outlined if a roentgenogram is made after the bronchi have been filled with iodized oil. A region of atelectasis is indirect evidence of bronchial obstruction and should cause one to suspect an endobronchial tumor. In 72 per cent of this series of cases an obstructing lesion of the bronchus was suspected on roentgenographic examination.

BRONCHOSCOPIC EXAMINATION

Although biopsy of a specimen obtained during a bronchoscopic examination is essential in determining the exact nature of any endobronchial lesion, these neoplasms generally present such a typical gross appearance that the bronchoscopist is frequently able to make a correct diagnosis from the gross appearance alone. There is partial or complete occlusion of the bronchus by a smooth, freely movable, soft, vascular mass, which may appear pink, red, or purple. The surface of this polypoid lesion is characteristically smooth and rarely ulcerated but slight contact may precipi-

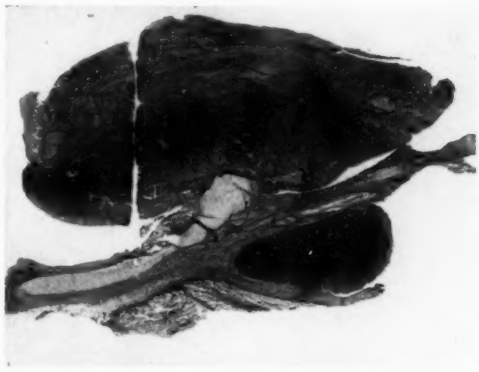

Fig. 1. A section through an adenoma of the bronchus, with the bronchial wall from which it has arisen. Note narrow pedicle and lack of bronchial or peribronchial spread. The mass of cells outside the bronchus is a lymph node ×3½.

Fig. 2. Adenoma of bronchus. The epithelium is intact overlying the neoplasm and there is bronchial and peribronchial extension of the tumor. An island of cartilage from the bronchial wall is seen in the tumor. Hematoxylin and eosin.

Fig. 3. Adenoma of bronchus. Gross specimen demonstrating residual tumor in the bronchus after endoscopic treatment by means of diathermy. Note the severe bronchiectasis.

tate rather marked bleeding. Usually there is no fixation or rigidity of the bronchial wall.

PATHOLOGY

Although adenoma of the bronchus presents an almost characteristic gross appearance, the final diagnosis must rest on positive microscopic evidence. In all of our 38 cases the diagnosis of adenoma of the bronchus was established by positive microscopic evidence. In 23 of the cases this was based on tissue removed endoscopically. In 15 of the cases (Table II) the lung, or a portion of the lung containing the tumor, was available for microscopic study, while in 2 cases necropsy material was also available.

Gross characteristics. The adenomas varied considerably in size, the smallest being 7 millimeters in diameter and the largest 8.5 centimeters in its largest diameter. The length and width of the pedicle attaching the tumor to the bronchus varied greatly. Generally, the site of attachment of the adenoma to the bronchial wall was narrower than the greatest width of the tumor. In 1 case this was very striking, as illustrated in Figure 1; the greatest diameter of this tumor was 1.8 centimeters but the pedicle at its attachment to the bronchial wall was only 3 millimeters in diameter.

There is a tendency for adenoma of the bronchus to infiltrate the bronchial wall and the peribronchial tissues. In 13 of the 15 cases in which the lung was available for study, there was invasion of the bronchial wall and peribronchial tissues (Fig. 2). In the remaining 2 cases there was no infiltration of the neoplasm into the bronchial wall peripheral to the cartilage, the main mass of tumor being within the bronchial lumen.

Adenomas invariably arise from the main stem or larger bronchi. The right side is more frequently involved than the left. In 23 of our cases, the lesion was located in the right lung and in 15 cases, in the left lung (Table I).

The condition of the lung distal to the neoplasm depends on the degree of bronchial obstruction which the tumor has produced. Various degrees of bronchiectasis were encountered. Since the neoplasm was usually situated in a large bronchus, bronchiectasis when present frequently involved a large portion of the bronchial system either of one lobe or occasionally of the entire lung. Pneumonitis invariably accompanied the bronchiectasis. In all but 2 of the 15 cases in which the lung was available for study there was some bronchiectasis. Example shown in Figure 3. In this case the adenoma had been fulgurated endoscopically and the bulk of obstruction removed. The bronchiectasis and pneumonitis remained, however, and were largely responsible for death.

No metastatic growths were found outside the thorax in the 2 cases of adenoma of the bronchus in which necropsy was performed. In 1 case only was a local hilus lymph node involved and that node was adjacent to the neoplasm.

Histologic features. There are many difficulties connected with the accurate histologic diagnosis of this type of neoplasm from a small specimen. Adenoma of the lung is likely to be confused with other lesions histologically. It must be differentiated from highly malignant small cell bronchiogenic carcinoma. This is important because of the vastly different prognosis of the two lesions. However, on a cellular basis it is not oftentimes easy to differentiate between these two lesions. Although the characteristics of the individual cells vary little in the two types of neoplasm, several differential features were found helpful. Mitotic figures can be found in the tumor cells of the bronchiogenic carcinoma type but are usually absent in the adenoma type. Degeneration of the tumor cells (pyknosis, karyorrhexis, and necrosis) is a much more common finding in bronchiogenic carcinoma than in adenoma.

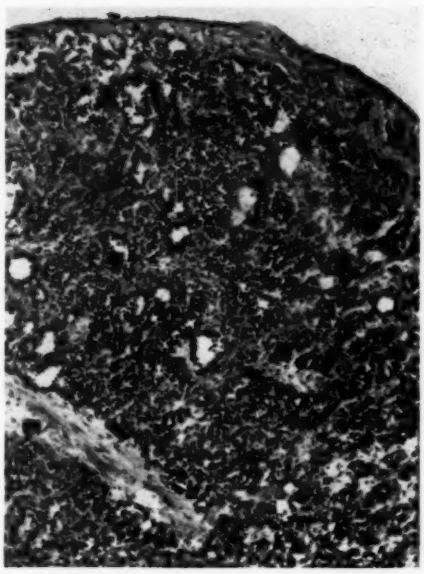

Fig. 4. Adenoma of bronchus. Biopsy specimen. Small cells with poorly formed acini. Hematoxylin and eosin, ×70.

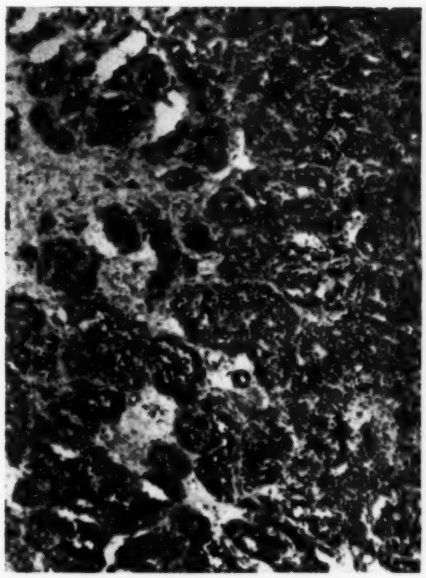

Fig. 5. Adenoma of bronchus from another patient. The histologic pattern resembles that of Figure 4. Hematoxylin and eosin, ×88.

Another lesion that must be differentiated from adenoma of the bronchus is the hyperplastic type of epithelium which is seen about infarcts of the lung (Sayre). This should not cause difficulty because infarcts usually occur in the periphery of the lung where adenomas are not seen. Because of its peripheral location, this lesion is encountered at necropsy but not bronchoscopically. A diagnosis of carcinoma in the region of an infarct of the lung should be treated with considerable skepticism.

The type of cell which is consistently present in adenoma of the lung is a fairly small, round, regular cell which does not have marked hyperchromatism of the nucleus. There is little variation in the size of the cells. We have been impressed by the remarkable histologic similarity of all 38 different adenomas. Mitotic figures were practically absent in the neoplastic cells in all cases.

The tumor cells consistently make an attempt to form acini but are rarely very successful in their attempt. The result is that the cells group themselves into alveoli or groups of cells which have a poorly formed lumen or else they group themselves into cords of cells (Figs. 4 and 5). Womak and Graham have considered that similarity exists between these tumors and mixed tumors of the salivary glands. The finding of cartilage and bone in the substance of these tumors is not difficult to explain, when one considers that invasion through the bronchial wall does occur and that the bronchial wall has cartilage in it which sometimes turns to osseous tissue.

Invasion of a lymph node was present in only 1 case. In this particular instance the involved lymph node was adjacent to the tumor, and it seems probable that this process does not represent metastasis, in the sense of a tumor embolism, but rather represents a direct invasion of the lymph node (Fig. 6). In no instance in this series did metastasis occur to the other lung or outside the thoracic cavity. Ultimately this feature differentiates the adenoma type of lesion from bronchiogenic carcinoma.

Between the groups and cords of epithelial cells there usually wasa thin stroma of connective tissue. In this stroma were found large numbers of thin walled blood vessels lined by endothelial cells. A noticeable feature of all adenomas of the bronchus has been their vascularity. It is no wonder that bleeding is a prominent feature in the clinical course of these neoplasms. In fact, many adenomas morphologically simulated neoplasms of blood vessels. The epithelium overlying the tumor was frequently intact although at times it was ulcerated. In one instance the tumor cells seemed

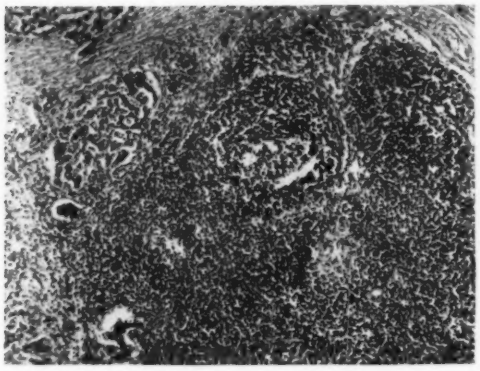

Fig. 6. Hilus lymph node, in a case of adenoma of bronchus, partially invaded in upper left hand corner from carcinoma. This appeared to be a direct invasion rather than an embolic phenomenon. Hematoxylin and eosin, ×60.

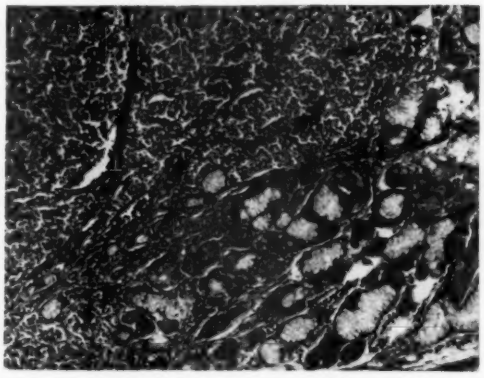

Fig. 7. This photomicrograph presents an adenoma of the bronchus. The cells of the tumor appear to be originating from the bronchial mucous glands. Hematoxylin and eosin, ×70.

to arise directly from the peribronchial mucous glands (Fig. 7). It seems probable that the surface epithelium of the bronchus, which is the usual source for the origin of bronchiogenic carcinoma, is not always, and indeed may never be, the source from which the adenoma originates.

Adenoma of the lung is in many ways similar to types of neoplasm in other parts of the body; namely, basal cell carcinomas (rodent ulcers), cylindromas, carcinoid tumors of the appendix and ileum, islet cell tumors of the pancreas and adenomas of the parathyroid. This similarity is based not only on the slowness of growth and tardiness to metastasize but also on morphologic grounds.

It is obvious from this study and others that adenoma of the lung is a neoplasm of the lung *sui generis*. It cannot be compared, in so far as prognosis is concerned, with bronchiogenic carcinoma, although occasionally it resembles bronchiogenic carcinoma. Morphologically, for the most part, the cellular picture is utterly different. The slowness of growth and low metastasizing factor are features of bronchial adenoma which remove it from the realm of bronchiogenic carcinoma. However, because of the fact that it has the potentialties of invading the peribronchial tissue and lymph nodes (Fig. 6) and because it can become a space-occupying lesion, obstructing the bronchus and thereby producing bronchiectasis and infection of the lung, bronchial adenoma is a lesion that if left untreated will eventually kill the patient. For these reasons it seems better to think of bronchial adenomas as malignant, thereby admitting their potentialities for killing the patient but at the same time sharply differentiating them from the ordinary type of bronchiogenic carcinoma.

PROGNOSIS

In studying the prognosis of cases of bronchia adenoma, it is interesting to divide the series into those in which treatment was surgical (pneumonectomy or lobectomy), and those in which treatment was more conservative (surgical diathermy, radium or roentgen rays). These data may be summarized from Table I. In 14 cases in which lobectomy or pneumonectomy was performed there was 1 death, or a mortality rate of 7.2 per cent. In 22 cases in which treatment was by means of surgical diathermy, radium or roentgen rays there were 2 deaths, or a mortality rate of 9 per cent. These 2 patients did not die directly as the result of the treatment but some months later of other causes. Two of the patients did not receive any treatment; one of these we have not been able to trace and at the time of writing, the other was still alive and well a year after his registration at the clinic.

TREATMENT

There is a difference of opinion among observers as to the most satisfactory method of treating bronchial adenoma. Generally, the decision rests between attempting endoscopic removal of the lesion and extirpation of the lesion by means of lobectomy or pneumonectomy. The method to be employed must necessarily depend on many factors, such as the patient's age and general state of health, the location of the tumor and especially its relationship to the coryna, the degree of second-

ary pulmonary suppuration and the degree of peribronchial infiltration of the adenoma. The fact that peribronchial infiltration is so prevalent in cases of adenoma of the bronchus would seem to favor lobectomy or pneumonectomy as the procedure of choice. On the other hand, lobectomy or pneumonectomy, even for adenoma of the bronchus, is still a very formidable procedure and one that as yet carries with it a definite element of risk. Furthermore, peribronchial extension of the adenoma of itself, as experience has demonstrated, is not always as serious a state as might be expected.

At the present time, it is our practice to employ the conservative form of treatment in those cases in which the adenoma is attached to the bronchial wall by a comparatively narrow pedicle, is movable, and is situated in a bronchus that can be adequately and thoroughly visualized bronchoscopically. The degree of peribronchial invasion is, as a rule, extremely difficult or impossible to evaluate from gross inspection. Bronchoscopic removal of the tumor is also indicated when the adenoma is situated so close to the coryna that surgical treatment would be inadvisable, and also when the general condition of the patient is such that lobectomy or pneumonectomy is unduly hazardous. The advantage of bronchoscopic removal lies in its comparative safety. It is imperative that patients thus treated be followed by at least yearly bronchoscopic checks to be certain that adenoma does not recur, as there is no other method to detect early recurrence.

Lobectomy or pneumonectomy is the procedure of choice when the adenoma is situated in a bronchus that cannot be adequately visualized bronchoscopically. It is generally preferable in those cases in which there is marked evidence of associated pulmonary suppurative disease. It is also preferable when there is obvious evidence of peribronchial infiltration or when an adenoma of the bronchus has been treated endoscopically and tends to recur.

The advantage of surgical removal of the tumor lies primarily in the fact that after the lesion has once been removed in this manner recurrences are extremely rare, whereas following endoscopic removal such recurrences are comparatively common. With the great strides that have been made in the field of thoracic surgery and the reduced surgical mortality associated with lobectomy or pneumonectomy for adenoma of the bronchus, we are employing this method of treatment with increasing frequency. The conservative form of treatment still has a definite field of usefulness, however, and still holds a very valuable place in treatment of adenoma of the bronchus.

At times it may be of advantage to combine the two methods of treatment. In Case 23, Table I, the adenoma was situated in the left lower lobe bronchus and was associated with marked secondary pulmonary suppuration. Surgical treatment seemed indicated and was employed. On exploration the lung was found bound down by a mediastinal mass that would not permit pneumonectomy or lobectomy. Subsequently, the tumor was destroyed by endoscopic means and the patient has remained well up to the present time with no evidence of recurrence.

The problem of treatment is further complicated by the fact that in certain instances favorable results may be obtained from roentgen therapy alone, as is well illustrated in Case 34, Table I, in which the patient is still alive and well 12 years after treatment, although the tumor itself is still present. Roentgen therapy as a rule does not seem to influence the size of the adenoma markedly, although at times it does seem to have a limiting effect on its development.

CONCLUSIONS

1. Adenoma of the bronchus is a relatively common tumor involving the tracheobronchial tree.

2. It occurs usually among younger persons than does carcinoma of the bronchus and, in contrast to bronchiogenic carcinoma, is more common among women than among men.

3. It is generally slow growing and usually gives rise to clinical symptoms over a much longer period then carcinoma of the bronchus before the diagnosis is established.

4. In our experience cough is the most frequent and earliest symptom of adenoma of the bronchus. Hemoptysis, asthmatoid wheeze and recurrent bouts of pulmonary infection are other common symptoms.

5. Adenoma of the bronchus generally presents a characteristic bronchoscopic picture, but the final diagnosis must rest on microscopic examination.

6. Adenoma of the bronchus presents a characteristic microscopic picture. Mitotic figures are usually absent. The type of cell is consistently a fairly small, roundish cell which does not have marked hyperchromatism of the nucleus. The tumor cells consistently make an attempt to form acini but are rarely very successful in the attempt. A noticeable feature of all adenomas of the bronchus has been their vascularity. In no instance in our series did metastasis occur to the other lung or outside the thoracic cavity. From our study we feel that adenoma of the bronchus should be regarded as a neoplasm of the lung *sui generis*.

7. The method of treatment to be employed in cases of adenoma of the bronchus depends on the situation of the tumor, the degree of secondary pulmonary suppuration and the patient's general condition. In our experience endoscopic destruction of the tumor and destruction by surgical extirpation of the tumor by means of lobectomy or pneumonectomy are the most satisfactory methods of treatment.

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AN EVALUATION OF THE COFFEY I METHOD FOR URETEROINTESTINAL ANASTOMOSIS

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THE many and varied procedures devised for transplanting the ureters into the bowel suggest that no highly satisfactory method is yet available. The Coffey I operation in our hands has been reliable, though not ideal. This technique probably is not the final solution of the whole problem, nor is our application of it perfected. This relatively old procedure has been overshadowed by emphasis on newer methods. Thirty-nine consecutive cases are here reported to demonstrate early results and to offer some comparison with reports on other methods. No attempt is made to discuss the general treatment of bladder cancer, exstrophy, and other conditions for which urinary diversion may be advisable.

The conditions for which transplantation might be done are common. Hence the technique preferably should be one readily mastered by the well trained surgeon. Some of the methods described in the literature seem to require unusual manipulative skill. If such highly specialized methods yield definitely superior results, then it behooves surgeons, and urologists in particular, to acquire the needed special skill. Upon reviewing the literature we find no method which has produced results superior to those following the Coffey I method as demonstrated clinically by a consecutive series of reasonable size. The Coffey I method is simple and direct. In general highly specialized techniques are less enduring than simple direct procedures. There are, of course, notable exceptions. Most reliable operations not only are based upon established surgical principles but also apply these principles as directly as the situation permits.

When the Coffey I procedure is used all steps may be visualized, so that the operator knows what is done. Manipulation of apparatus via the rectum, intraureteral cutting, dependence on the necrotizing effect of a suture, and the like, represent essentially blind maneuvers. With the Coffey III (1, 2, 7) and Higgins (6) operations, the cutting through of the special necrotizing suture must occur or complete failure results. This fact is recognized by some proponents of such methods who have advised placing gauze or a tube in the lower bowel and including this gauze or tube in the necrotizing sutures. Then, if the cut-through is not forthcoming, traction on the packing or tube is added—an essentially blind maneuver. With Jewett's method (11, 12) the formation of the actual stoma is accomplished solely by touch and is tested by passing rigid sounds through the elastic bowel and ureteral walls. Tangential cuts have been made with Jewett's instrument, with disastrous results from leakage. To avoid some of these difficulties, Jewett has devised a set of bulb sounds. He also advised inflation of the rectum with air and more extensive mobilization of the bowel. In passing, one not uncommon fault of the highly specialized methods is that the procedure may become more and more complex with each "perfection."

Manipulation and contamination can be reduced to a minimum, particularly when both ureters are transplanted at one operation. Of the last 20 cases in our series only 1 was done in two stages. The Higgins and Jewett operations require two stages to complete any one anastomosis (though the first stage of both sides is usually done at the first operation; while at the second, the anastomosis is completed bilaterally and often other surgical procedures are carried out). Adhesions encountered at the second stage have been a major problem, but careful attention to avoid peritoneal injury has greatly reduced this hazard (12). With the Coffey I method, however, any one anastomosis is completed at one stage and does not have to be dissected and handled again. Manipulation tends to decrease blood supply and increase the possibility of soiling. As will be noted later, deficient blood supply underlies many failures. Abscess formation is not due to the inevitable slight soiling (which the peritoneum readily overcomes), but rather to sloughs, massive soiling, and the leaving of an open fistulous communication with the peritoneal cavity.

No foreign bodies remain in the lumen of the urinary tract. Catheters increase the hazard of

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Fig. 1. Autopsy specimen of a patient surviving 44 years and 8 months after bilateral ureterosigmoidostomy for exstrophy by Fowler. N.Y.H. No. 225 529.

infection. They may become plugged, thus defeating their aim of producing good drainage. Furthermore, they may compress the blood supply of the ureter and lead to sloughing with subsequent leakage. The Coffey II method (1, 2, 7) is the classic example of ureterosigmoidostomy with the use of catheters. McComb (14) and G. G. Smith (17) strongly favored the results of the Coffey I over the II method, after trying both operations. The experimental use of vitallium tubes in the anastomosis to insure patency was not successful, largely due to calculus formation (21). Any permanent foreign body in the urinary tract greatly increases the hazards of stone formation and intractable active infection. However, early adequate urinary output per rectum should be obtained. Other factors permitting, a plan which accomplishes this with the best ultimate result, the least risk, and the minimum number of operations is the procedure of choice. In this series both ureters were transplanted in one operation 23 times; in all of these cases urine was recovered within 6 hours and the majority had urine in the rectum at the end of the procedure. Those who had spinal anesthesia showed less delay than those who had general anesthesia. In the entire series of 39 cases all upper tracts which functioned preoperatively continued to function in the immediate postoperative period. Two upper tracts, which had no function by intravenous pyelography before transplant, regained good function after the operation. Theoretically the Coffey III method and some of the two stage methods might produce renal damage before the stoma functioned adequately. Practically, however, this appears to be absent or insignificant.

The wide area of contact afforded the ureter and bowel by the long wide submucosal trough provides adequate adherence to prevent leakage, allows for some collateral circulation between the two organs to lessen the possibility of dangerous sloughs, and promotes adhesions which should take tension away from the site of critical union. This is true of all methods utilizing Coffey's main principles: Coffey's operations, Higgins', Jewett's, Hinman's, Foley's, and others. It is not true of the Maydl and Bergenhem (4, 13) operations and, while some beautiful results have been obtained by these operations, they have been generally unreliable and are now seldom used. Also the Maydl and Bergenhem operations are unsuitable in a program for bladder cancer, since a portion of bladder remains attached to the ureter.

The valve action for which Coffey devised the submucosal trough is an additional advantage, but the presence or absence of the valve action cannot always be correlated with the clinical results. If a patient lives 44 years and 8 months after operation, works regularly, and raises a family, his transplantation is certainly a clinical success. Autopsy was obtained on such a patient but no valve action could be demonstrated (Fig. 1). The operator, Fowler (5, 20), attempted to obtain valve action by attaching both ureteral ends to the upper surface of a tongue of bowel mucosa which would be pressed upward by bowel content and thus occlude the ureters. This method did, however, provide a wide area of contact. From the autopsy specimen one would not suspect that the valve mechanism had only recently given away. Also the patient was not invalided until shortly before death.

With the Coffey I operation no specially constructed instruments are necessary, the usual laparotomy selection being sufficient. The instruments devised by Hinman (8) and Foley (3) apparently did not become popular. Jewett's special electrotome (11) is the best known device in current use. Aside from any special skill or knowledge needed for proper use, the instrument itself must be obtainable and kept in good condition to be of any value. Expense, while of minor importance, cannot be ignored. Special instrument-

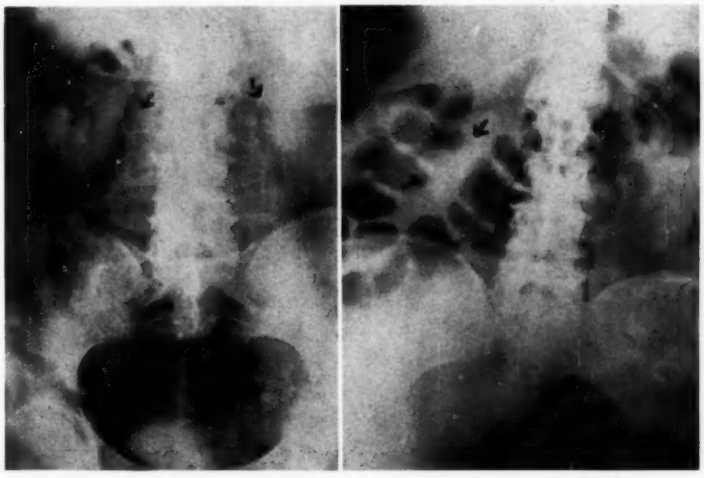

Fig. 2. Intravenous pyelogram before, left, and after, right, transplantation. Function is present in the right kidney though the ureter on this side leaked. The left pyelogram we consider satisfactory. N.Y.H. No. 372 347.

sometimes show a tendency to multiply themselves: for example, into sets of varying caliber or varying curvatures. Again, a method using special instruments should show clearly superior results to the simple direct Coffey I to warrant the expense, extra training, and trouble in obtaining and using that tool.

Ureteral angulation should be avoided as it may interfere with blood supply as well as urinary drainage. Any portion of the bowel from the descending colon to the rectum can be used. The bowel may be mobilized if necessary. There is, however, less latitude on the right side than on the left and hence a greater length of ureter is necessary on the right to permit a nonangulated course. The right side was always transplanted first in this series.

Absence of ureteral tension, a *sine qua non* to success, is readily accomplished by the Coffey I method. Tension decreases ureteral blood supply and tends to make the anchoring suture cut through. The operator should bear in mind that traction on the ureter during dissection temporarily lengthens it. Some excess length must also be allowed for mild bowel and ureteral motion. Lack of redundancy between the lowest retroperitoneal fixation of the ureter and the anastomosis is, we believe, one of the common causes of failure.

Relative immobilization of the operative site is obtained by tacking a flap of parietal peritoneum over the anastomosis. Peristalsis is not altered, but gross displacements of the bowel which could pull or angulate the ureter are prevented. In

Fig. 3. Autopsy 37 days after right ureterosigmoidostomy, and 26 days after left transplantation. Death from peritonitis due to right ureter sloughing away from bowel. Left side satisfactory. N.Y.H. No. 372 347.

Fig. 4. Postoperative intravenous pyelogram showing satisfactory condition on the right but with left hydronephrosis. Left anastomosis leaked leading to death. M.H. No. 39125.

addition the anastomosis is partially or wholly extraperitonealized, which may be advantageous in prevention of general peritonitis in case of leakage. We have had little experience with extraperitoneal techniques but on theoretical grounds, unrecognized tension might result when the bowel is allowed to drop back toward its normal position. Fecal and urinary fistulas seem more common after the extraperitoneal methods.

What then are the results obtainable with the Coffey I operation, since after all the real value of an operation lies in its results?

Our postoperative mortality is 10.2 per cent. We include every death regardless of cause occurring between operation and the time for hospital discharge. Priestley and Strom from the Mayo Clinic report a mortality of 15.7 per cent with 51 cases, using the Coffey I operation by an extraperitoneal technique. Jewett using his own method indicates a 33 per cent mortality in 33 cases, but the mortality in his last 10 cases was only 10 per cent. The last 15 patients in our series of 39 had bilateral transplants without a mortality.[1] Hinman (10) in 1936 in a complete review of the literature concluded that the operative mortality for ureterointestinal transplantation done for all reasons and by the various methods had been about 30 per cent; but in cancer cases alone the rate was much higher, usually nearly 50 per cent. Our hospital mortality with the Coffey I method seems reasonable compared with other reports, but 39 is not a large enough series to allow the conclusion that this method is definitely superior. However, considering the 51 cases from the Mayo Clinic and our 39, all done by the Coffey I method, mainly on cancer patients, it seems permissible to conclude that the operative mortality from the Coffey I procedure is about 13 per cent. This mortality is less than that reported on any other large series by another method. A 13 per cent mortality, nevertheless, is rather high; and most particularly does it appear so since the operation is so often a preliminary to further major surgery, such as total cystectomy.

Of our 4 postoperative deaths, 2 were directly due to failure of the operation.

F.W., N.Y.H. No. 372 347, a 58 year old white female, was found to have extensive carcinoma of the bladder. Diversion of the urinary stream was done in 2 stages because of difficulties resulting from marked obesity. The right ureter was transplanted to the lower sigmoid November 30, 1943. Aside from a temperature elevation to 37.8 degrees on the first day after operation, the course was afebrile and satisfactory in other respects. Urine output was adequate and equal from bladder and rectum. The left ureter was transplanted on December 11, 1943 (11 days later). The course was again satisfactory for another 11 days. Right upper abdominal pain and anorexia then appeared, followed by a spiking temperature. Three days after the onset of pain, jaundice began. Both kidneys continued to function by intravenous pyelograms (Fig. 2) and urine output remained adequate until the 23d day after the second operation when anuria supervened. Death occurred 3 days later.

Autopsy (Fig. 3) revealed that the right ureter had separated from its attachment to the bowel and had drained directly into the peritoneal cavity. The opening into the bowel had healed completely, being marked only by black silk sutures. A generalized fibrinous and urinous peritonitis was present. A huge abscess occupied the subhepatic region; this probably accounted for the jaundice. The long interval (21 days) between transplantation and evidence of trouble suggests poor blood supply and sloughing as the underlying cause. It is possible that this region may have been disturbed during the period of the second operation.

J.R., M.H. No. 39125, a 60 year old male with epidermoid carcinoma of the bladder had bilateral ureterointestinal transplantation August 12, 1943, under continuous spinal anesthesia. The postoperative course was entirely satisfactory in every respect for 10 days when temperature elevation and signs of sepsis began. On the 12th postoperative day, an abscess containing urine about the left transplant was drained surgically but the patient continued a downhill course in spite of all supportive measures, and died on the 15th day after transplantation. Urine output remained excellent to the last. Blood urea nitrogen the 9th postoperative day was 8 milligrams per cent but rose to 39 on the day of death. On the 12th day after operation was carried out intravenous pyelography (Fig. 4) revealed good function on both sides at 15 minutes and with hydronephrosis on the left. Autopsy was not permitted.

[1]Since this was written, February 1945, an additional consecutive 6 patients have had bilateral transplantation without a death, making a total of 21 consecutive cases without hospital mortality, though not without complications.

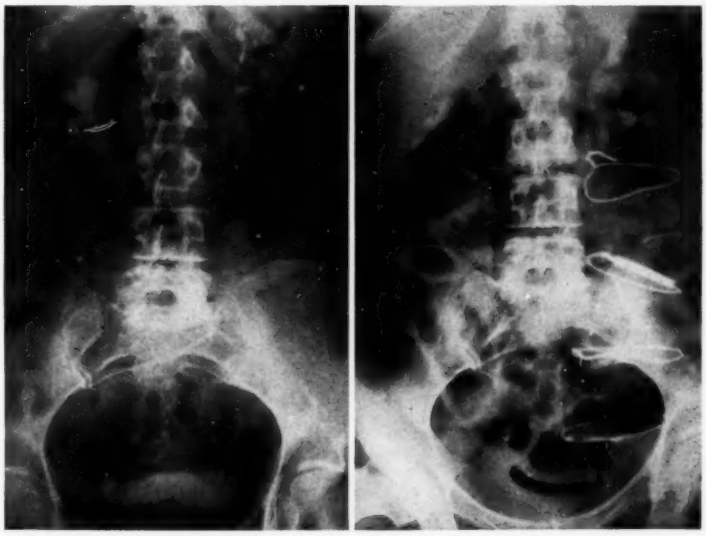

Fig. 5. Preoperative, left, and postoperative, right, intravenous pyelograms showing bilateral function and intermediate degree of hydronephrosis. Death due to carcinomatosis. N.Y.H. No. 310 862.

In both these cases leakage occurred after at least 1 week. This fact suggests that the ureter had sloughed. The operative and autopsy findings indicate the same. Probably the commonest cause of leakage is failure of blood supply to the ureter leading to slough. Of course, actually leaving an open communication with the peritoneum at operation will allow leakage but any method which does this with regularity will be abandoned abruptly. Also if such does occur, the signs of leakage should on the average appear much earlier than in our instances. If the ureter is said to have "sloughed out" the failure of blood supply seems obvious, but if the ureter is said to have "pulled out" the idea conveyed is that traction *per se* was the cause. Sutures cut through by ischemic necrosis. Tension reduces ureteral blood supply, and also pulls on the anchoring suture (in effect tightening it). Yet, if there is no failure of blood supply, we believe sutures will not cut through and healing should proceed. Moreover, breaking or untying of anchor sutures must be rare. Thus "sloughing out" and "pulling out" of the ureter are both due to ischemia in the final analysis. Unless infection is very virulent and thus necrotizing by reason of toxicity, local failure of blood supply is the ultimate cause of sloughing from infection. Also as noted before, leakage is not due to the contamination occur-

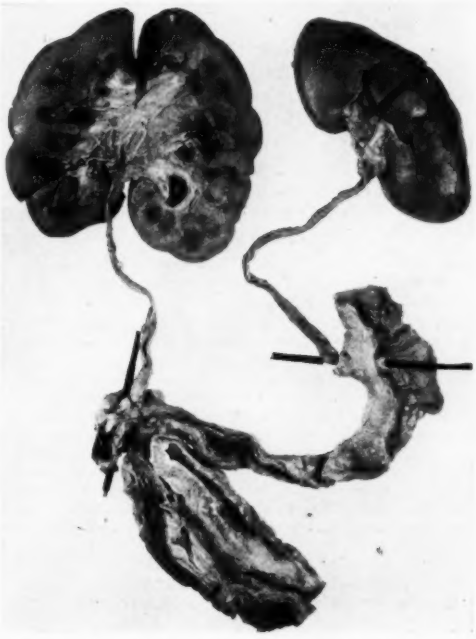

Fig. 6. Autopsy specimen showing adequate anastomoses. N.Y.H. No. 310 862.

Fig. 7. Autopsy specimen 12 days after bilateral transplantation showing intact anastomoses. Note proctitis about sloughing stump of right ureter. Death due to cardiac failure. M.H. No. 72805.

Fig. 8. Postoperative intravenous pyelogram (5 minute exposure) after removal of temporary left nephrostomy, showed prompt appearance of dye in both pelves. L.L.G., N.Y.H. No. 330 761.

ring in the properly done operation. We have 1 other patient who developed an abscess, after discharge from the hospital (see case J.B., N.Y.H., No. 358 646, described under the late complications).

The other 2 of the 4 deaths in this series were not due to local failure of the operation. In both the urinary tracts functioned well as indicated clinically, as shown by intravenous pyelogram, or as demonstrated at autopsy. The first case was done for palliation and in retrospect was poorly chosen. The second likely would not have died had postoperative care been better.

H. M., N. Y. H. No. 310 862, a female aged 44 years, had an extensive invasion of the bladder from carcinoma of the cervix resulting in complete urinary incontinence. Diversion of the urinary stream offered alleviation of distressing symptoms. The right ureter was transplanted June 24, 1943, followed by a febrile course and unsatisfactory output of urine from the rectum. A chest x-ray film 6 days later revealed pulmonary metastases. By the 8th postoperative day, however, the urinary output had increased to equal that from the untransplanted ureter. The urinary drainage through the sloughing perineal mass continued to be distressing, and the other ureter was transplanted July 22, 1943. The course was again febrile and on the 14th day after the second transplant the abdominal wound separated down to the peritoneum. The edges showed no attempt at healing. Death occurred on the 17th day (Fig. 5).

Autopsy (Fig. 6) revealed practically no healing activity around the recent operative wounds. Metastatic carcinoma was present in the vagina, pelvis, bladder, mesentery, omentum, long bones, and lungs. A large abscess was present in the pelvis associated with the carcinoma (not the transplants), and an empyema occupied the left chest. The urinary tracts were in good condition without undue dilatation, but mild pyelonephritis was found microscopically. No leakage was present.

B. L., M. H. No. 72805, a 63 year old female with epidermoid carcinoma of the bladder, had bilateral ureterointestinal anastomosis March 6, 1944. Following operation urinary output remained always over 1000 cubic centimeters each 24 hours. The blood urea nitrogen was 13.9 milligrams per cent before operation and was 18.3 on the 7th postoperative day. Pulse became elevated and at times irregular. Dyspnea was marked. One episode of pulmonary edema occurred. Digitalis and other measures to combat cardiac disease were used. Both transplants were explored on the 8th postoperative day, but no abnormality was found. The patient died on the 12th postoperative day. Autopsy found both transplants in good condition (Fig. 7). The pathologist's report states: "Carcinoma of bladder . . . Acute arteriosclerotic heart failure resulting in massive bilateral pulmonary edema. This is undoubtedly the immediate cause of death."

In retrospect, the cardiac condition was not adequately treated. Particularly the fluid intake was not lowered. A preoperative electrocardiogram had found only tachycardia and moderate left ventricular preponderance. This finding gave us a false sense of security and caused us to center our attentions on the possible failure of the transplants. All considered, the fatal outcome was clearly not due to any failure of the operation itself but was due to erroneous postoperative management.

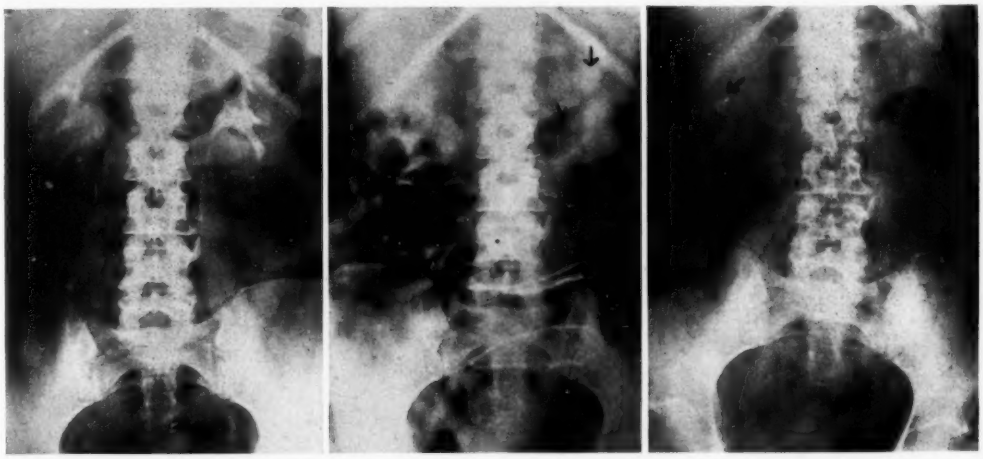

Fig. 9. Preoperative, left, and postoperative, middle, intravenous pyelograms showing excessive bilateral hydronephrosis. A calculus has formed in the right pelvis since operation, also. A.T., N.Y.H. No. 360 395.

In the reported series the nonfatal postoperative complications are often not mentioned and only seldom described. A perusal of case histories when included, however, indicates that nonfatal complications are by no means rare—in fact, in some series they are more the rule than the exception. Our total complication rate, including both fatal and nonfatal, was 23.0 per cent. The nonfatal complications numbered 5, or a rate of 12.8 per cent. We define postoperative complication as any untoward occurrence between operation and the time of discharge which has added a hazard to or prolonged an expected smooth convalescence. In other words, 77 per cent of the patients in this series had a satisfactory recovery in the hospital. The nonfatal postoperative complications are outlined in the following. There were no fecal fistulas at any time. At a second admission, one ureter was made to drain temporarily to the exterior by operation (case J. B., N.Y.H. No. 358 656, described later). Except this 1 instance, there was no urinary drainage from any wound. No patient had permanent urinary diversion except the transplantation.

N. F., N. Y. H. No. 396 305, a 75 year old female, had a simultaneous bilateral ureterointestinal anastomosis on October 3, 1944. The postoperative course was satisfactory until the 14th day when on getting out of bed for the first time dyspnea and cyanosis suddenly appeared. Treatment for pulmonary embolus was immediately begun, and symptoms subsided over the next 6 days. A total cystectomy for carcinoma of the bladder has subsequently been done. Although considered a poor risk from the start, she survived two major operations and a serious pulmonary embolus. She is now asymptomatic and cares for herself.

G. R., N. Y. H. No. 352 907, a 68 year old male with extensive infiltrating carcinoma of the bladder, had a bilateral ureterointestinal transplant on March 25, 1943 for palliation. The patient had a chronic cough and was in poor general condition. Progress was entirely afebrile and satisfactory until the 6th postoperative day when without previous warning patient was found to have several loops of bowel protruding through the abdominal incision. The wound was reclosed within an hour after it was discovered, and no apparent systemic reaction ensued. Patient was discharged 32 days after the original operation, voiding per rectum. He has since died of carcinomatosis.

L. L. G., N. Y. H. No. 330 761, a female aged 40 years, had the ureters transplanted to the bowel because of severe chronic submucous cystitis. The right ureter was transplanted on January 20, 1944. Urine output from the rectum was consistently about half that from the bladder; aside from this the course was satisfactory. Intravenous pyelograms 12 days later revealed delayed function and hydronephrosis on the right. The blood urea nitrogen remained normal. Following the left anastomosis on February 5, 1944, however, nausea appeared and the blood urea nitrogen slowly elevated to 40 milligrams per cent. On February 14, 1944, intravenous pyelograms showed delayed output and hydronephrosis on the right, and no evidence of function on the left in 45 minutes. Urine output per rectum varied from 100 to 3500 cubic centimeters per day. Because of persistent nausea and vomiting and persistence of nitrogen retention, a left nephrostomy was done, February 24, 1944, followed by a prompt disappearance of symptoms and return of blood urea nitrogen to normal. When the nephrostomy tube was removed, March 19, 1944, the wound closed without leakage. Subsequent intravenous pyelograms show prompt appearance of dye in both pelves and diminishing hydronephrosis (Fig. 8). There has been one attack of left pyelonephritis which occurred 3 months after patient left the hospital. She now works daily and is clinically well.

A. T., N. Y. H. No. 360 395, a 53 year old white woman, had a bilateral ureterointestinal anastomosis in 2 stages because of a huge vesicovaginal fistula. The right side was transplanted July 15, 1943, the left August 6, 1943. After

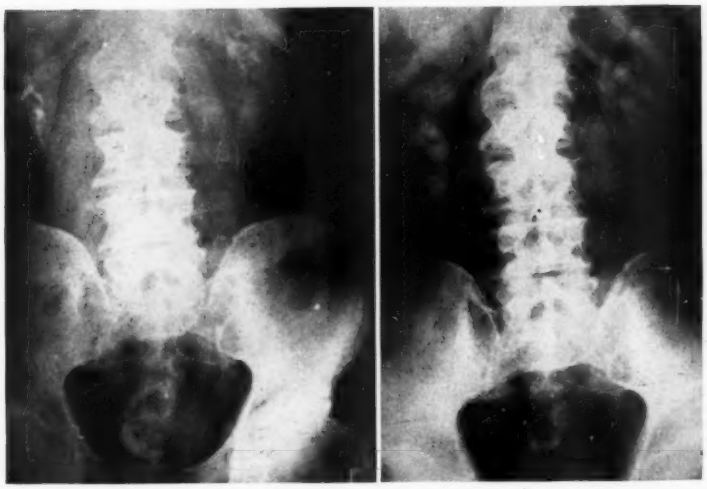

Fig. 10. Preoperative, left, and postoperative, right, intravenous pyelograms showing satisfactory pyelographic result, in spite of the fact that an abscess about the right transplant was soon discovered. Right nephrectomy. Recovered.

the first operation the urine output per rectum was 50 cubic centimeters the first 24 hours, but steadily increased to 1500 or 2000 cubic centimeters per day after 10 days. Intravenous pyelograms then revealed marked hydronephrosis and delayed function on the right. Because of this fact an interval of 3 weeks was allowed before transplantation was carried out on the other side. The blood urea nitrogen remained normal during this period. There was a febrile period of 4 days following the second operation, but urinary output appeared to be adequate. The blood urea nitrogen elevated to 55 milligrams per cent by the 6th postoperative day, then slowly returned to 25. Subsequent intravenous pyelograms have shown marked bilateral hydronephrosis and delayed function.

We consider this our worst result from a pyelographic aspect (Fig. 9). The patient has remained symptom free, however, and is clinically well. The blood, urea nitrogen checked at intervals in the Out Patient Department has varied from 35 to 61 milligrams per cent, the most recent was 35. A calculus has formed in the right kidney, this being the only incidence of stone formation except for 1 patient whose renal calculi were removed by us before transplantation and who has had a recurrence since the ureterointestinal anastomosis.

J. M., N. Y. H., No. 373 934, a 56 year old male with traumatic urinary incontinence, was subjected to bilateral ureterointestinal anastomosis. The right transplant was done December 7, 1943. The course was febrile and urinary output per rectum was unsatisfactory. The blood urea nitrogen rose from 22 to 38 milligrams per cent. Transplantation of the left ureter was postponed 3 weeks to allow improvement. Following the second stage, output per rectum remained satisfactory (1500 to 4000 c.c. per day). Two weeks later the blood urea nitrogen was 56 milligrams, next day 9 (laboratory error?), and subsequently 23. Eight days after the 2nd operation the wound became reddened, later was opened and drained pus, not urine, from superficial tissues.

What results were obtained regarding the urinary tract proper? Apparently transplantation of one ureter and ligation of the other is not a rare urological practice. It is our opinion that these patients sooner or later need all the functioning renal tissue it is possible to conserve. Ligation of one ureter condemns that side to nonfunction and necessarily defeats one of the most important aims of urology: namely, preservation of the best possible renal function. If the side to be ligated is nonfunctioning and irreparably damaged there may be some justification. We can imagine unusual circumstances where transplantation of one of the ureters might be impossible but no such condition was met in this series, which includes palliative cases. Valuable function has returned after operation sufficiently often in our series to make us always try to transplant both ureters. The added risk seems slight compared to the possible gains. If one side is ligated and the transplant fails, disaster obviously follows—a risk not so slight. Also it is not uncommon for the ligated side to cause trouble, for example, pyonephrosis.

These 39 patients had 79 ureters (the right side of one being double); 75 of these functioned by

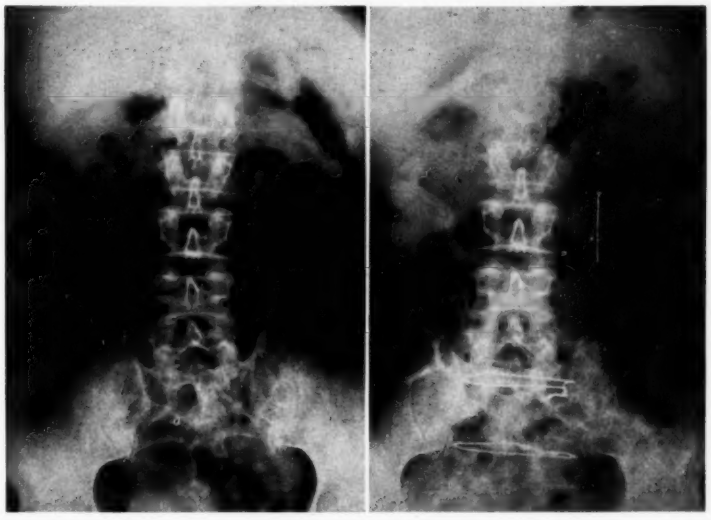

Fig. 11. Preoperative, left, and postoperative, right, pyelograms showing return of function on the right after transplantation. The barest trace of function was observed in the right kidney on the second attempt at pyelography preoperatively but only on the 120 minute film. No functional return on the left. C.L., N.Y.H. No. 320 144.

intravenous pyelogram before operation and 77 did so after operation. The 4 patients dying postoperatively had 8 functioning upper tracts, even though 2 of these transplants leaked, as discussed previously. After the original discharge two kidneys became nonfunctioning as judged by intravenous pyelogram, and a nephrectomy was performed on another. The history indicates that one other patient died of renal failure 9 months after discharge. These last 3 cases and several that showed a definite improvement in function are outlined in the following.

R. F., N. Y. H. No. 371 654, an 8 month old male, had a complete exstrophy of the bladder. The renal status was apparently normal as demonstrated by intravenous pyelograms and function tests. On November 30, 1943, the right ureter was transplanted to the lower sigmoid through a right rectus incision. The postoperative course was entirely satisfactory. Although definite measurement was impossible, it appeared that the urinary output per rectum was approximately equal to that from the left ureter. The patient left the hospital 2 weeks after operation to recuperate from a cold, with the understanding that he would be readmitted within 2 to 4 weeks for the second stage.

He was not heard from until a follow-up letter was written 5 months later. He was readmitted with the story that urine stopped coming from the rectum 2 to 3 weeks after leaving the hospital. Hence, the right kidney had not functioned for over 4 months.

The left ureter was transplanted May 25, 1944, through a left McBurney incision. Postoperative course was satisfactory, and the patient had a normal left intravenous pyelogram October 13, 1944. The right kidney still shows no function by intravenous pyelogram.

J. B., N. Y. H. No. 358 656, a 61 year old male, was subjected to bilateral ureterointestinal anastomosis because of extensive malignant papillomatosis of the bladder, in preparation for cystectomy. Both ureters were transplanted in one stage, June 22, 1944. Some difficulty was encountered because of marked obesity, particularly of the mesosigmoid. Abdominal distention marked the course for the following 9 days, but the urine output was adequate. On the 18th day he had an episode of unexplainable chills and fever which subsided over a period of 5 to 6 days with bed rest, liquid diet, and sulfadiazine.

The patient was readmitted August 4, 1944 for cystectomy. Intravenous pyelograms showed excellent function and only minimal bilateral hydronephrosis (Fig. 10). On the evening after admission all of the typical signs of acute appendicitis appeared. Exploration revealed several small abscesses between the loops of the intestines. The very friable ureter (which was probably surrounded by abscess near the anastomosis) was accidentally torn off. A catheter was inserted into the ureter and brought out through the wound and the abscesses were drained. He went home with one ureteral catheter. When it came out and could not be reinserted, the partial obstruction resulted in pyonephrosis which was treated by nephrectomy November 2, 1943.

He was readmitted December 3, 1943, with severe unexplained jaundice. No specific therapy was given. The jaundice subsided slowly and the patient's general condition improved steadily. He has subsequently gained weight and returned to work. He is clinically well, but the bladder tumor is still present. Extensive radiation therapy has been given.

C. L., N. Y. H. No. 320 144, a 62 year old male with multiple carcinomas and diverticula of the bladder, had simultaneous bilateral ureterointestinal transplant on

Fig. 12. Preoperative, left, and postoperative, right, intravenous pyelograms showing return of function in the left kidney. M.D., N.Y.H. No. 337 234.

October 10, 1944, and cystectomy on October 31, 1944. Before operation two attempts were made to make intravenous pyelograms. Function was so diminished, however, that dye appeared in the right kidney in weak concentration only after 2 hours, and none in the left. Phenolsulfonphthalein was excreted poorly (17 per cent in 1 hour). Bilateral upper urinary tract infection was also present. Following operation the course was remarkably good, there being no elevation of temperature or pulse. Intravenous pyelograms on November 13, 1944, revealed restoration of function in the right kidney (Fig. 11). Dye appeared in good concentration in 5 minutes. No definite evidence of function could be determined on the left.

M. B., N. Y. H. No. 337 234, a male farmer aged 62 years, was found to have a large infiltrating carcinoma of the bladder. Intravenous pyelogram revealed a normal right kidney and nonfunctioning left upper urinary tract on August 20, 1942. On September 1, 1942, the right ureter was transplanted to the lower sigmoid. There is no record of urinary output from the bladder subsequently. The left ureter was transplanted to the upper sigmoid September 8, 1942. At operation the ureter was tensely dilated and over 1 centimeter in diameter. The course was afebrile after both operations. Urinary output was satisfactory from the rectum and continued about the same after the second procedure. Intravenous pyelograms September 26, 1942, 16 days after the second ureter had been transplanted revealed prompt appearance of dye bilaterally and mild bilateral hydronephrosis (Fig. 12). The blood urea nitrogen remained normal throughout the hospital course.

This case is an example of improved renal function following ureterointestinal transplantation.

Only 2 patients have had blood urea nitrogen concentrations consistently above 30 milligrams per cent. One of these died of leakage postoperatively and the elevation was more likely due to general sepsis and reabsorption than actual failure of the renal parenchyma (Case M. H. No. 39125 previously described). The other patient remains clinically well and she is pleased with the result though we are not (Case N.Y.H. No. 360 395 previously described).

The long term outcome of the operation regarding renal function cannot be foretold from this study. We have noticed, however, that many pyelograms a few months after operation show improvement over the ones taken at 2 or 3 weeks. A clear indication of the future is particularly difficult when most of the late deaths have been due to cancer. Thus of the 11 patients now known to be dead after leaving the hospital, 9 died of cancer, 1 of uremia (Case N.Y.H. No. 373 934), and 1 of phlebitis (here reported).

M. F., N. Y. H. No. 394 888, a 63 year old female, had a bilateral simultaneous ureterointestinal anastomosis on September 12, 1944. Two ureters were present on the right and being rather closely attached to each other by vessel-bearing tissue both were implanted into a single trough. It was necessary to free the sigmoid from its attachments and move it to the right to obtain satisfactory position for anastomosis. The subsequent course was satisfactory. A mild fever subsided over a 4 day period and urinary output was immediately adequate. Intravenous pyelograms after operation showed prompt function but mild hydronephrosis in all three renal pelves (Fig. 13).

Cystectomy for carcinoma of the bladder was followed by an afebrile course. It became necessary to treat hypoproteinemia and avitaminosis after the second operation but the patient was discharged in good condition. Two

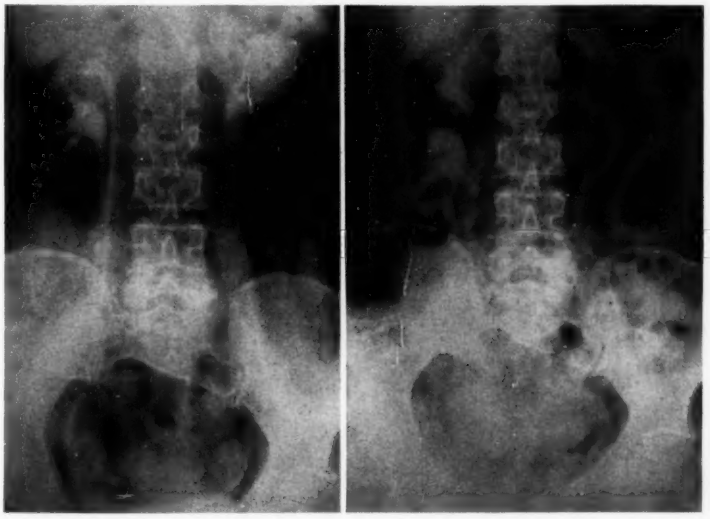

Fig. 13. Preoperative, left, and postoperative, right, intravenous pyelograms showing two right ureters. M.F., N.Y.H. No. 394888.

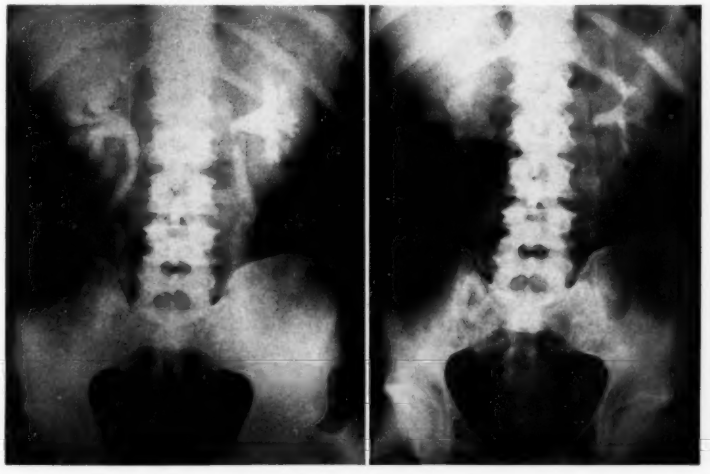

Fig. 14. Preoperative, left, and postoperative, right, pyelograms illustrating good result on both sides (the right hydronephrosis and function was unchanged and the left improved).

weeks later the right leg became swollen, and a low grade fever appeared. On readmission blood urea nitrogen, serum protein, and carbon dioxide combining power were normal. Intravenous pyelograms showed no interval change. After a 10 day period in which lower abdominal pain and tenderness appeared, the abdomen was explored. No free fluid or inflammatory masses were present and the serosa was surprisingly free of adhesions. The two right ureters were not visibly dilated, and the right kidney was normal to palpation and movable. The region of the right anastomosis was encased in a fibrous adhesion attached to the pelvic wall. No evidence of urinary extravasation or abscess formation was discovered. The patient died suddenly 24 hours after exploration. Autopsy was not permitted. It is believed that she died of pulmonary embolus originating in a right iliac thrombophlebitis.

Fig. 15. Autopsy specimen on patient whose pyelograms are illustrated in Figure 14. Death was due to pulmonary collapse at cystectomy on subsequent admission. N.Y.H. No. 312 417.

The procedure in all cases was the Coffey I operation with particular attention to the following.

A complete diagnosis and general evaluation was always made. Intravenous pyelography usually sufficed, but repeated or retrograde studies were made when necessary to a clear diagnosis on the status of the upper tracts. A barium enema, while perhaps not essential always, has been of value. It allows the operator to plan his method of procedure. In at least 1 instance ureteral transplantation was contraindicated because of extreme diverticulosis plus signs of bowel infection. If bowel symptoms should appear after ureteroenterostomy the known preoperative condition of the organ would be most advantageous. The functioning capacity of the anal sphincter should be determined. Usually the history and digital examination are sufficient but if in doubt testing by enemas is in order.

Bilateral simultaneous transplantation was done whenever feasible. Twenty-three or 59 per cent, of the 39 cases were so done, with 2 deaths: a mortality of 8.7 per cent, compared to 12.4 per cent mortality in the 16 done in separate operations. This difference is not significant because a change of only 1 mortality from the second to the first group would make these items 13.0 and 6.2 per cent, respectively. No complications were attributed to the single stage plan.

Preoperative preparation of the bowel is most important. The usual regimen was: 5 to 6 days on 8 to 12 grams sulfasuxidine daily; enema every

Fig. 16. Preoperative, left, and postoperative, right, pyelograms illustrating satisfactory pyelographic result. N.Y.H. No. 311 423.

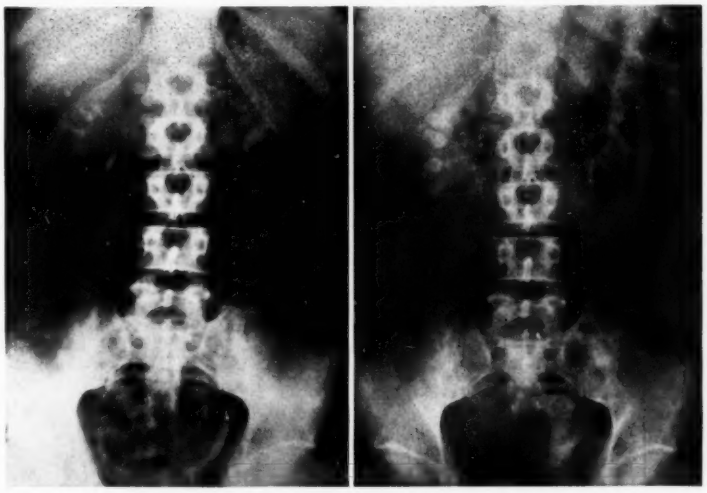

Fig. 17. Preoperative, left, and postoperative, right, pyelograms illustrating good result on left and intermediate result on right. The right has subsequently become nonfunctioning and is counted a "poor" result. N.Y.H. No. 373 304.

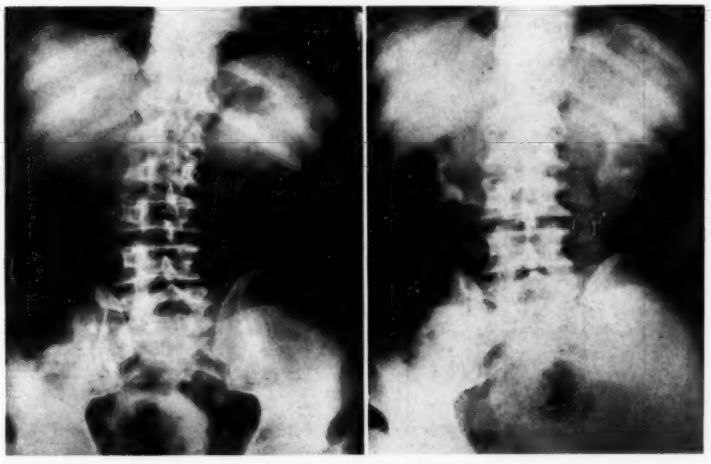

Fig. 18. Preoperative, left, and postoperative, right, pyelograms showing good result. N.Y.H. No. 381 456.

other day; cathartic (usually citrate of magnesia 250 c.c.) on alternate days; and a low residue diet. The diet was reduced to clear fluids the day before operation, and both an enema and the cathartic were given. Also sulfadiazine 0.5 gram 4 times a day was started the day before.

Anemia, avitaminosis, etc. are appropriately treated before operation.

Choice of anesthesia has varied, but in general continuous spinal has been quite satisfactory.

An infusion is given during operation, and usually a transfusion.

At operation the following are emphasized: good exposure, gentle handling, obtaining an adequate length of ureter, protecting ureteral blood supply, arranging the anastomosis to be

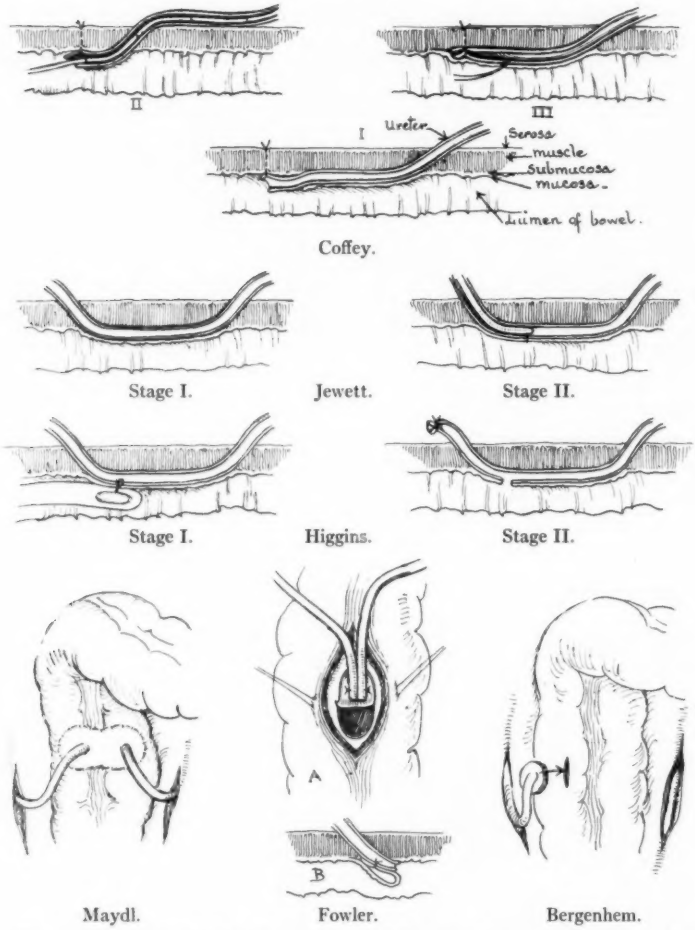

Fig. 19. Diagrams showing general plans of the more common ureteroenterostomies.

without tension, suturing which is merely approximating, and partially immobilizing the site of transplant. The ureter becomes temporarily lengthened during dissection and the bowel is often displaced from its natural locale—facts to be borne constantly in mind. We invert the first suture line and the site of the anchoring suture with a second line of interrupted fine silk sutures. Special care must be taken that the upper end of the anastomosis is not closed tightly about the ureter by making the suture lines too long.

We have not hesitated to transplant dilated ureters. None of the ureters in this series were massive: i.e. more than 2 centimeters in diameter. Several were over 1 centimeter in diameter. We have the impression that results with moderately dilated ureters are somewhat better. Probably the ureteral blood supply is larger and the extra size allows for shrinkage and fibrosis, yet leaving ultimately a good caliber.

After operation a large rectal tube is kept in place constantly for from 5 to 12 days. This tube is changed twice daily, and more often if not draining. Changing is done to insure patency and also because a shift in position often improves drainage. This decompression relieves pressure

TABLE I.—ANALYSIS OF 39 PATIENTS WITH COFFEY I TRANSPLANTS

	No.	Per cent
Indication for operation		
Genitourinary cancer	34	
Exstrophy of bladder	2	
Nonmalignant fistulas	2	
Panmural cystitis	1	
Average age—53.12 years		
Youngest—8 months		
Oldest—76 years		
Deaths	4	10.2
Due to failure of operation (Case MH No. 69125 and NYH No. 372 347)	2	5.1
Due to other causes (Case MH No. 72805 and NYH No. 310 862)	2	5.1
Complications		
Fatal and nonfatal	9	23.0
Nonfatal	5	12.8
Pulmonary embolus (Case NYH No. 396 305)	1	
Wound separation (Case NYH No. 352 907)	1	
Obstruction requiring temporary nephrostomy (Case NYH No. 330 761)	1	
Excessive bilateral hydronephrosis (Case NYH No. 360 395)	1	
Wound infection (Case NYH No. 373 934)	1	
Patients discharged	35	
Pyelonephritis after discharge (all recovered)	3	
Calculus formation since discharge (one had calculi removed before transplantation)	2	
Deaths since discharge	11	
Causes Carcinoma	9	
Renal failure (Case NYH No. 373 934)	1	
Phlebitis (Case NYH No. 394 888)	1	
Patients still living	24	61.6
Followed 3 to 47 months.		
Blood urea nitrogen above 30 mgm. % at any time	7	
Blood urea nitrogen permanently above 30 mgm. % (NYH Nos. 372 347 and 360 395)	2	

TABLE II.—ANALYSIS OF 79 COFFEY I TRANSPLANTS

	Patients	Per cent
Ureters transplanted	79	
Number functioning kidneys by intravenous pyelograms immediately preoperatively	75	
Number functioning kidneys by intravenous pyelograms immediately postoperatively	77	
Number functioning kidneys by intravenous pyelograms at time of discharge (4 patients with 8 functioning kidneys died)	69	
Number of transplants failing after discharge	4	
Uremic death (1 patient, but 2 transplants)	2	
Nonfunction, cause unknown	2	
Simultaneous bilateral transplants (22 patients)	44	
Ureters transplanted at separate operations (16 patients)	32	
Three ureters transplanted simultaneously (1 patient)	3	
Results on basis of intravenous pyelograms (Figs. 14–18)		
Good	37	46.9
Intermediate	32	40.5
Poor	10	12.6

on the suture lines, promotes output, and decreases possible mild rectal reabsorption. Enemas and irrigations are contraindicated since they increase intrabowel pressure. Rarely a mild cathartic is indicated about the 10th day. A low residue diet is continued for 2 weeks. Sulfadiazine 0.5 grams 4 times a day is given for about 2 weeks to lend a bacteriostatic quality to the urine. Usually a Wangensteen gastric drainage is started immediately after operation and used intermittently for 2 or 3 days. This procedure prevents distention which we found troublesome in many cases before its use. Finally an intravenous pyelogram is made to check the result.

SUMMARY

The Coffey I operation for ureterosigmoidostomy has the following good characteristics: it is relatively simple and follows fundamental principles directly; no extraordinary surgical skill is needed; no special instruments are required; no foreign bodies remain in the urinary tract; immediate urinary output can be expected; clear visualization of all steps may be obtained; the ureter and bowel adhere well; tension and angulation are avoidable; relative immobilization is possible; any one side is completed at one stage; and the early results are fairly satisfactory, comparing favorably with results obtained by other methods.

Our results with 39 consecutive patients are indicated (Tables I and II). The operative mortality from all causes was 10.2 per cent; the mortality due to local failure of the operation, however, was 5.1 per cent. The nonfatal hospital complication rate was 12.8 per cent. Seventy-seven per cent of the patients had a satisfactory postoperative course in the hospital. Preoperatively by intravenous pyelography there were 75 functioning upper tracts; postoperatively in the hospital 77 functioned. At this writing, 3 to 47 months after operation, 24 patients (61.5 per cent) are still alive and have 44 functioning upper urinary tracts.

A total hospital complication rate of 23 per cent, fatal and nonfatal, is too high especially in view of the fact that the procedure is so often a preliminary to further drastic therapy. However, the desperate plight of most of the candidates

provides considerable justification. The symptomatic relief is often sufficient indication.

We have attempted to limit discussion to ureterosigmoidostomy itself and purposely avoided discussions of treatment of bladder cancer, exstrophy, fistula, etc. If ureteral transplantation to the bowel were a benign, highly successful procedure it, no doubt, would be very widely used.

These operations were performed in the years 1941 to 1944, inclusive, by 7 operators using essentially the same technique, the Coffey I operation. Only one of the operators had had previous experience with ureteroenterostomy. The surgeons were: at the New York Hospital, Stevens, A. McLellan, Drew, Whitmore, Gardner, and Marshall; at the Memorial Hospital, Twombly and Marshall. None of these case records, except the one by Fowler's method (20), has been previously reported.

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SURGERY OF THE MANDIBLE: THE AMELOBLASTOMA

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THE ameloblastoma develops from the cells of the enamel organ during a particular phase of tooth development. It is found most frequently in the mandible, less so in the maxilla, and occasionally in the pituitary gland, tibia, ulna, and ovary. For the purposes of this report only the ameloblastoma of the mandible will be considered. Although this tumor is considered to be uncommon there have been over 400 reported (1, 4, 5, 6). Both sexes are affected in about equal frequency. The ameloblastoma has been recognized at birth and as late as the seventy-sixth year, the average age in Robinson's series was 37.6 years (6).

The ameloblastoma is generally described as a benign neoplasm although in a study of 379 tumors, 4.5 percent showed metastases or histologic evidence of malignancy (6). A better known characteristic of this tumor is its persistence and tendency to "recur" after operative intervention. The tendency for the ameloblastoma to "recur" locally is probably due to inadequate surgical treatment. The purpose of this report is to consider (1) the surgical treatment of ameloblastoma of the mandible and (2) the reconstruction necessary subsequently.

BRIEF SUMMARY OF DENTAL HISTOGENESIS

A brief review of dental histogenesis will facilitate understanding the origin not only of the ameloblastoma but also of other dental anomalies (Table I). Tooth development may be divided into three stages: (1) growth, (2) calcification, and (3) eruption. For the purpose of this report only the first stage (growth) will be considered. This stage can be further subdivided into (a) initiation, (b) proliferation, (c) differentiation, and (d) apposition (Fig. 1).

Initiation. Between the sixth and seventh weeks of intrauterine life an inward proliferation of the oral epithelium, *O.ep.*, begins (Fig. 1a). This is the dental anlage, *D.a.* If initiation does not occur there will be no tooth development and anodontia will be the clinical condition (2).

Proliferation. Cellular proliferation continues until an invagination takes place and the connective tissue which borders the invaginated epithelial portion condenses and forms the dental papilla, *D.p.*, the primordium of the dentin and pulp (Fig. 1b). During this period the early form of the odontome arises.

Differentiation. The enamel organ, *En. org.*, which originates from the invaginated epithelium gives rise to the outer enamel epithelium, *O.e.e.*, the stellate reticulum, *S.R.*, the stratum intermedium, *S.I.*, and the inner enamel epithelium, *I.e.e.* (Fig. 1c). It is during this period that the ameloblastoma arises from the enamel organ. This occurs within the first few years of life although no activity may become manifest until some years later. Enamel is never found in this tumor. If tooth development continues normally, however, the inner enamel epithelium will differentiate into ameloblasts, the enamel forming cells. Thus one can readily see that ameloblastoma is not the correct term because the tumor arises from the enamel organ before the ameloblasts have differentiated. The term preameloblastoma is more accurate.

In addition the odontoblasts differentiate from the adjacent connective tissue of the dental papilla. The dentinoenamel junction which forms the basic pattern of the tooth is determined between the inner enamel epithelium and the adjacent connective tissue of the dental papilla (Fig. 1d). It is during this period that the Hutchinson incisor and mulberry molar develop (9).

Apposition of dentin and enamel. In this stage a cusp of dentin is formed and with this stimulus the preameloblasts change to functioning ameloblasts and a corresponding amount of enamel is formed on the outer portion of the dentinoenamel junction (Fig. 1e). When this formation has been initiated, there is a synchronous recession of the odontoblasts and ameloblasts from each other. Incremental layers of enamel are apposed one on top of the other until the cusp is fully formed. Subsequent layers are apposed at the sides until the crown is complete (Fig. 1f). Systemic disease during this period sometimes affects enamel formation (7, 8). After formation of enamel has ceased, formation of dentin continues to complete the root.

DIAGNOSIS

Clinical findings. The ameloblastoma which is most frequently seen in young adults, is characterized by a slow progressive swelling of the jaw, usually near the angle. The tumor sometimes at-

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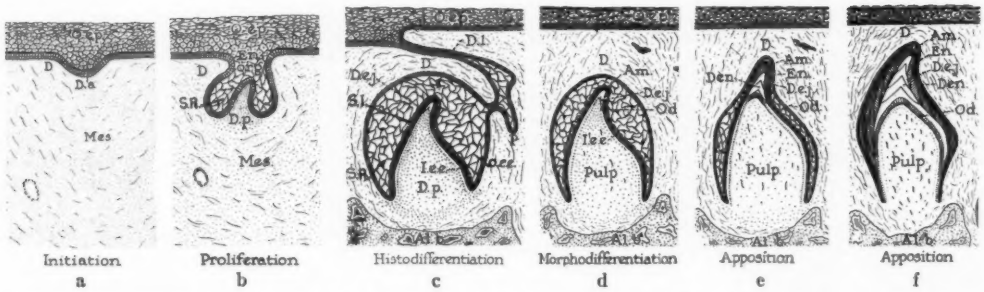


Fig. 1. Diagrammatic representation of the embryology of the lower human deciduous central incisor (modified from Sarnat and Shaw, 9). *O. ep.*, oral epithelium; *D.a.*, dental anlage; *D.p.*, dental papilla; *En org.*, enamel organ; *o.e.e.*, outer enamel epithelium; *S.R.*, stellate reticulum; *S.I.*, stratum intermedium; *I.e.e.*, inner enamel epithelium; *D*, deciduous incisor; *P*, permanent tooth bud; *Mes.*, mesenchyme; *D.e.j.*, dentino-enamel junction; *D.l.*, dental lamina; *Al.b.*, alveolar bone; *Am.*, ameloblasts; *Od.*, Odontoblasts; *En.*, enamel; *Den.*, dentin.

tains large proportions (Figs. 2a, 3a, 4), extends toward the clavicle and weighs several pounds. The growth may be accompanied by pain. There is usually a history of a tooth or teeth having been extracted from the area several years previously and of several attempts surgically to eliminate the tumor. Fistulous tracts leading to the oral cavity and secondary infection of the tumor are not uncommon.

The buccal plate of bone is usually expanded most, although the lingual bone may be expanded to push the tongue to the opposite side of the mouth. The bone is sometimes so thinned that it will crack like an eggshell. These are late findings, after the tumor has changed from the solid to the cystic phase. The patient may be seen only after pathologic fracture has occurred. Only occasionally do true signs of malignancy appear.

Roentgenographic findings. The roentgenogram serves as a valuable adjunct in the diagnosis of cystic lesions of the jaw, but the final diagnosis depends on the gross and particularly the microscopic examinations. The roentgenogram is most valuable for the early diagnosis of ameloblastomas of the jaw when the tumor is still centrally located, has not expanded the bone, and is in the solid phase. It is at this time, when most of the mandible is as yet not destroyed, that the tumor can be removed completely with no serious deformity resulting to the patient. When the ameloblastoma has become cystic and considerably larger, the clinical findings are obvious and the roentgenogram is of primary value in showing the extent of bone destruction (Figs. 3a and 4a). There is no constant characteristic roentgenographic description of the ameloblastoma (Fig. 5). The multilocular appearance and the scalloped border are by no means pathognomonic. The ameloblastoma, giant cell tumor, carcinoma, and other lesions which are destructive cannot be positively differentiated from each other on the roentgenogram (3).

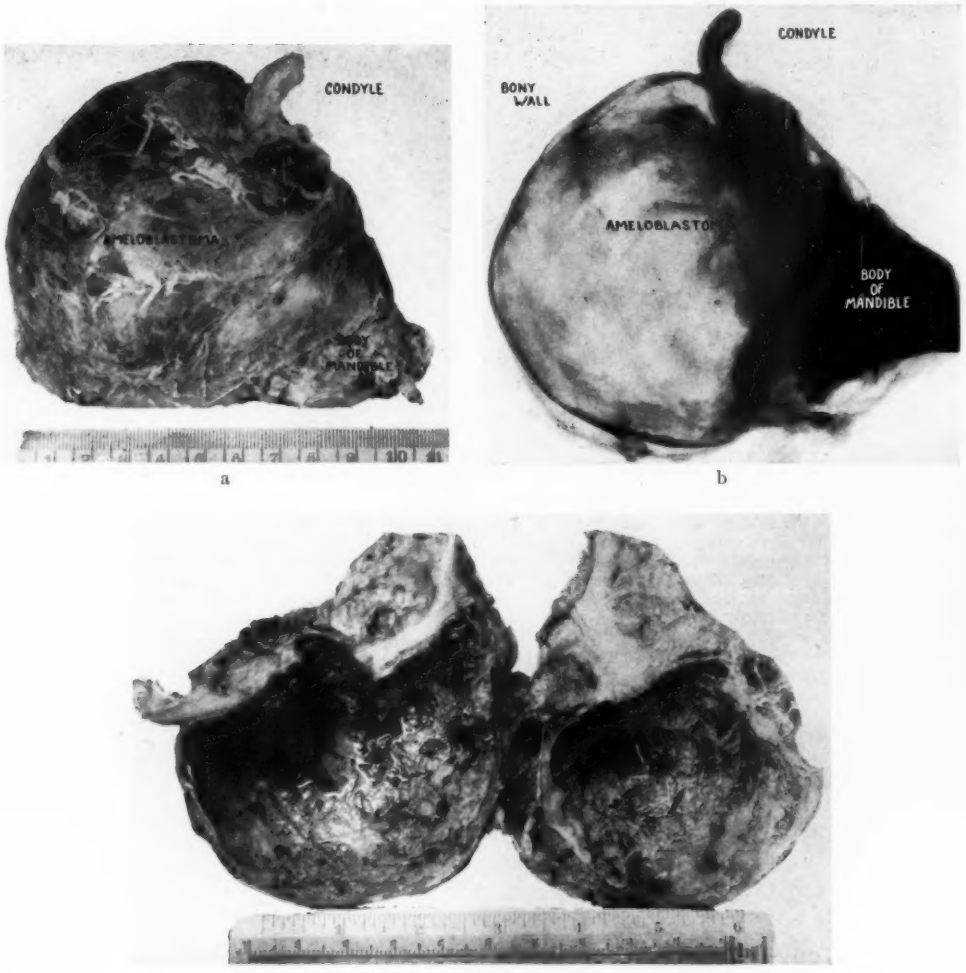
Gross findings. The findings on gross examination vary with the stage of development of the ameloblastoma. Analysis of 219 cases revealed that 57.5 percent were cystic, 24.2 percent were both cystic and solid, and 19.1 percent were solid (6). This classification is arbitrary and combinations of the solid and cystic tumors are found in varying degrees. The solid tumor which usually represents an earlier stage in development is of fine granular consistency, and encapsulated. There may be one principal mass with numerous smaller daughter areas. The cystic type usually represents the solid tumor after cystic degeneration (Fig. 4c). The contained fluid may be clear yellow to red and either of a mucous or serous consistency. The bone is expanded and may be parchment thin (Fig. 4b).

Microscopic findings. Interpretation of the microscopic findings in the ameloblastoma is facilitated by an understanding of the histology of the enamel organ (Fig. 1). Thoma states there are many variations due to the stage of differentiation the epithelium may attain when the tumor formation began, the behavior of the stroma, and the malignant changes which may develop (Table II). Malignant degeneration, although uncommon, does occur (Fig. 6).

Simmons states that where the cuboidal cells predominate, the growth is more malignant than in the cystic type with well developed ameloblast-like cells. Schweitzer and Barnfield believe that there is no apparent correlation between the histologic pattern of the ameloblastoma and its ability to metastasize.

Fig. 2. a, left, Photograph taken on May 10, 1943, of a patient with a large ameloblastoma of the right side of the mandible. F. R., white male, aged 43 years, was first seen by us in May, 1943. Swelling was first noticed inside right side of mouth in 1915. The mass continued to grow and patient had at least three local intraoral operations. In 1938 the right side of the jaw suddenly began to swell and at that time the mass was about 6 centimeters in diameter. The mass has continued to grow. In 1939 a diagnosis of ameloblastoma was finally made. Patient was told at that time that the operation would be worse than the disease and was told to go home and forget about it. When the patient was seen in 1943 he had been unable to work for the past few years. A hemisection of the mandible was done on May 11, 1943. He has worked ever since his recovery from the operation and has enjoyed good health. b, Postoperative photograph taken on May 25, 1943, after resection of the mandible.

Fig. 3. Roentgenograms of same patient as in Figure 2. a, left, Preoperative. Note the large mass on the right side of jaw and face. b, Postoperative, after resection of right half of mandible.



a b c

Fig. 4. Photograph, a, and roentgenogram, b, of the tumor and mandible which were resected. In b note the distortion of the condyle, ramus, and angle of mandible and absence of coronoid process. c, Photograph of specimen after it was cut in two. Note the large single cyst, the smaller cysts and solid tumor.

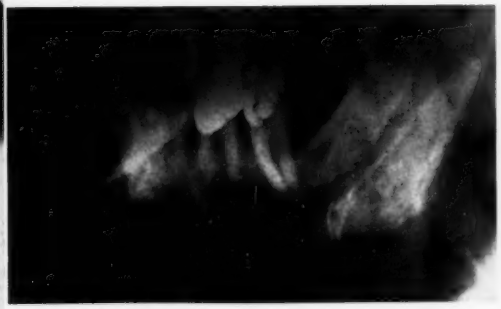
SURGICAL TREATMENT

Inasmuch as radiation does not affect the ameloblastoma materially, the treatment of this tumor of the jaw is primarily surgical. Both the surgical approach and the procedure which is carried out depend not only upon the diagnosis of the type of tumor but also upon its extent. In some instances the extent of the tumor will be such as to determine the type of surgical approach. In other cases, it is first necessary to know the type of tumor with which one is dealing and to determine, subsequently, the surgical approach and procedure on the basis of this knowledge. Clinical examination and roentgenographic studies will sometimes be adequate to make the diagnosis. However, in a large group of mandibular tumors diagnosis will still not be certain even after examining both patient and roentgenograms (3)

a

b

c



d

Fig. 5. Lateral roentgenograms of the mandible each showing different characteristics of the ameloblastoma. Although none of these are similar, each was proved to be an ameloblastoma on microscopic examination. (d, Courtesy, C. V. Mosby Co.)

In this latter group either preliminary biopsy or examination of a frozen section at the time of operation is of advantage. An accurate microscopic diagnosis will give the operator courage to do a radical operation if necessary or will give him confidence in the less radical procedure. However, it has not been our practice routinely to do a resection of the jaw in dealing with the ameloblastoma. The more accessible lesions are first removed locally. The patient is warned that repeated postoperative examinations will be necessary over a long period of time to discover possible extension of the tumor. In many instances this local excision is adequate and not deforming. In other instances (1) where a large portion of the mandible is involved, (2) where the tumor has definitely invaded beyond the confines of bone, or (3) where inaccessible areas of the mandible are involved so that local excision could not be adequate, resection of the mandible is the primary treatment of choice (Figs. 2 and 3). Sometimes the choice of whether to do a local excision or radical resection must be made only after surgical exposure of the area of involvement. Especially is this true where the surgical approach is from the outside through the neck. In almost every instance where the surgical approach is from the inside of the mouth, local removal is done.

Intraoral approach. Having made the decision to do a conservative local removal rather than a resection of the mandible, adequate exposure must be gained by freeing overlying soft tissues and attached mucoperiosteum over the complete extent of the tumor. Following this, overlying bone should be removed adequately, so as to give a complete exposure of the underlying tumor and

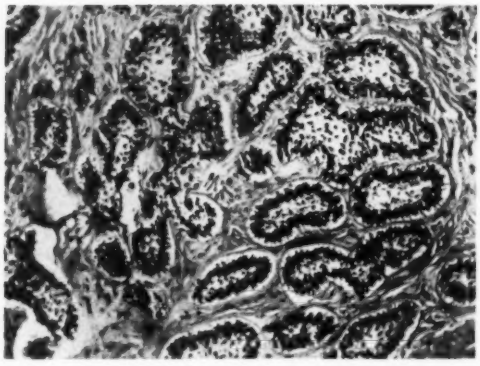


Fig. 6. Photomicrograph of a malignant ameloblastoma (of the jaw) which eventually metastasized to the lungs. Note the characteristic arrangement of the stellate cells with poorly defined cytoplasmic boundaries. These are surrounded by columnar cells which are hyperchromatic and do not possess the regular arrangement usually encountered in the more slowly growing type of ameloblastoma. The epithelium is arranged in irregular groups surrounded by dense collagenous stroma which tends to form a pseudo-basement membrane (September 16, 1940).

O. N., colored female, aged 23 years, was first seen on May 23, 1928, with the complaint of swelling of left side of face for 1 year. A diagnosis of ameloblastoma was made and it was removed through an intraoral approach without resection of the mandible. Patient next returned in 1935 with recurrent swelling of mandible and was reoperated upon. Radium was subsequently implanted (2232 mg. hours). Nodules soon appeared along ear, orbit, and forehead and eventually involved the entire left side of head. Patient began to vomit blood in 1939 and examination of the chest plate revealed multiple nodules in both lung fields. Necropsy was performed in 1942 and histologic examination of the tumor in the lungs revealed it to be morphologically identical with the tumors in operative specimens (10).

to permit partial obliteration of the cavity which results from the removal of the tumor. This obliteration is accomplished by collapse of soft tissue into the cavity. It is preferable not to rupture the capsule of the tumor itself during the operation. In many instances of the less loculated type of tumor the growth may be removed completely and without spillage. Under these circumstances there is less possibility of continued growth of the tumor.

Many of the multilocular tumors have irregular outlines and crevices in the bone at which point the tumor is usually broken into during the process of removal. One should never start out to do a curettement removal of this type of growth. It is much better to attempt total enucleation where possible. In multilocular or more invasive tumors one can become involved in a piecemeal removal of the tumor, however, and a certain amount of curettement will be necessary. Under these circumstances it is obvious that small fragments of growth will be left behind and necessitate removal at a later date.

To prevent this difficulty, cauterization of the cavity has been recommended. This cauterization may be either chemical or thermal. In general, the criticism of chemical cauterizing agents is that one cannot accurately determine the depth of penetration of the chemical so that cauterization tends to be either too great or too little in extent. The

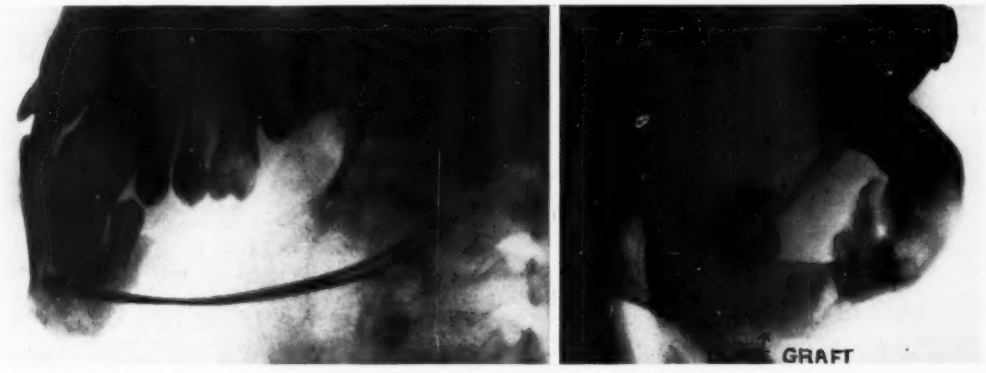


Fig. 7. a, left, Lateral roentgenogram of mandible after subperiosteal resection showing one method by which position of mandibular fragments can be maintained prior to insertion of bone graft. A stainless steel bar was inserted through drill holes in the bone. It has now been present for over 8 months, the wound has healed and bony union has occurred. In another instance a stainless steel bar was extruded after 4 years without suppuration. b, Lateral roentgenogram of the mandible after resection, stabilization of mandibular fragments, and insertion of bone graft. The opposite side of the jaw has been wired in occlusion and an attached splint is holding the posterior fragment in position.

TABLE I.—STAGES OF TOOTH DEVELOPMENT DURING WHICH CERTAIN DENTAL ANOMALIES FIRST APPEAR

Stages of tooth development	Dental aberration
I. Growth	
a. Initiation	Anodontia
b. Proliferation	Odontome
c. Differentiation	
Histodifferentiation	Preameloblastoma (Ameloblastoma)
Morphodifferentiation	Hutchinson incisor, Moon molar
d. Apposition	Chronologic enamel aplasia (Enamel hypoplasia)
II. Calcification	Fluorosis
III. Eruption	Pseudoanodontia

TABLE II.—HISTOLOGIC CLASSIFICATION OF THE AMELOBLASTOMA (12)

Type of ameloblastoma	Chief characteristics
1. Epithelioma	Little differentiation of epithelium which grows in cords or strands
2. Stellate	Epithelial cells stellate in shape; grow in sheaths or contained in follicles
3. Ameloblastic	Cylindrical cells (preameloblast) lining follicles
4. Acanthoma	Stellate reticulum differentiates into squamous or prickle cells, epithelial pearl formation
5. Carcinoma	Squamous cell

TABLE III.—VARIOUS APPLIANCES USED TO CONTROL FRAGMENTS OF MANDIBLE AFTER RESECTION

I

Appliances which utilize teeth (intraoral): posterior fragment contains teeth

*a. Interdental wires
*b. Arch bars
*c. Swaged metal splint (with or without jack-screw).
d. Splint on teeth with dependent part separating bone.

II

Appliances which utilize bone and teeth (intraoral and extraoral): short edentulous posterior fragment

a. Wire teeth in occlusion and use modeling compound in molar area to keep posterior fragment down.
*b. Arch bar or splint with posterior fork to keep posterior fragment down.
*c. Arch bar or splint on mandible with posterior portion accurately fitted to junction of body and anterior border of ramus. (Herpin splint with or without jack-screw)
*d. As in (c) except arch bar or splint applied to maxilla with interdental wiring.
e. Arch bar or splint with posterior part attached:
  1. Directly to bone.
  2. To bone screw.
f. Wire passed through drill hole near angle of mandible and attached posteriorly to head cap and wire rest of jaw in occlusion.

III

Appliances which utilize bone (intraoral and extraoral): Number of teeth and size of posterior fragment not necessarily a consideration

†a. Bone screws (and bar) inserted with each fragment. (Stader, Berry, Griffin, etc.)
  1. Intraoral.
  2. Extraoral (preferred).
b. Kirschner wires (modified) passed through fragments.
c. Bar passed through drill holes in end of each fragment.
*d. Open bite splint attached with circumferential wires.

*Also controls fragments adequately for insertion of bone graft.
†Not ideal for bone graft because of local osteomyelitis around bone screws and subsequent loss of stability of splint.

extent to which penetration goes and destruction is brought about with the thermal agent is better regulated than with the chemical. If the ameloblastoma has not been removed completely, it has been our practice to use the electro surgical unit or Bovie knife with the coagulating current and to go over the exposed bone surface. Heavier cauterization is done in areas of greater contamination with tumor tissue. The disadvantage of this procedure is that a certain amount of bone will be devitalized and sequestration will occur. In the meantime, the presence of the devitalized bone will delay healing. However, if the tumor and its immediate bony confines have been completely removed or destroyed cure is almost sure to result.

Extraoral approach. The external approach for both resection of the mandible and for local excision of the growth is the same. This incision should parallel the natural fold in the skin of the neck. It should be made underneath the mandible and should be adequate in extent to give complete exposure. The course of the lowest branch of the facial nerve in the neck should be remembered. This nerve can be preserved if the approach is carefully planned. The incision should be marked on the skin with the head in a normal position and should be 2 centimeters below the angle of the mandible. A flap containing skin, subcutaneous tissue, and platysma is then elevated. This includes the lower pole of the parotid gland and soft tissues anterior to it. Unless the lower pole of the parotid is elevated with this tissue the facial nerve must inevitably be severed. The entire ramus as well as the angle and most of the body may be thus exposed. Having exposed the area of the tumor, removal may be done in one of three ways. The procedure of local removal by shelling out the tumor and applying the cauterizing agent may be followed in certain cases. In other instances it is possible to do a partial block resection of the mandible; the Albee saw is used to remove the tumor and a containing block of bone, but a bridge of bone is left to maintain the continuity of the mandible. This is rarely feasible. The third method is to resect the mandible (Figs. 2 and 3).

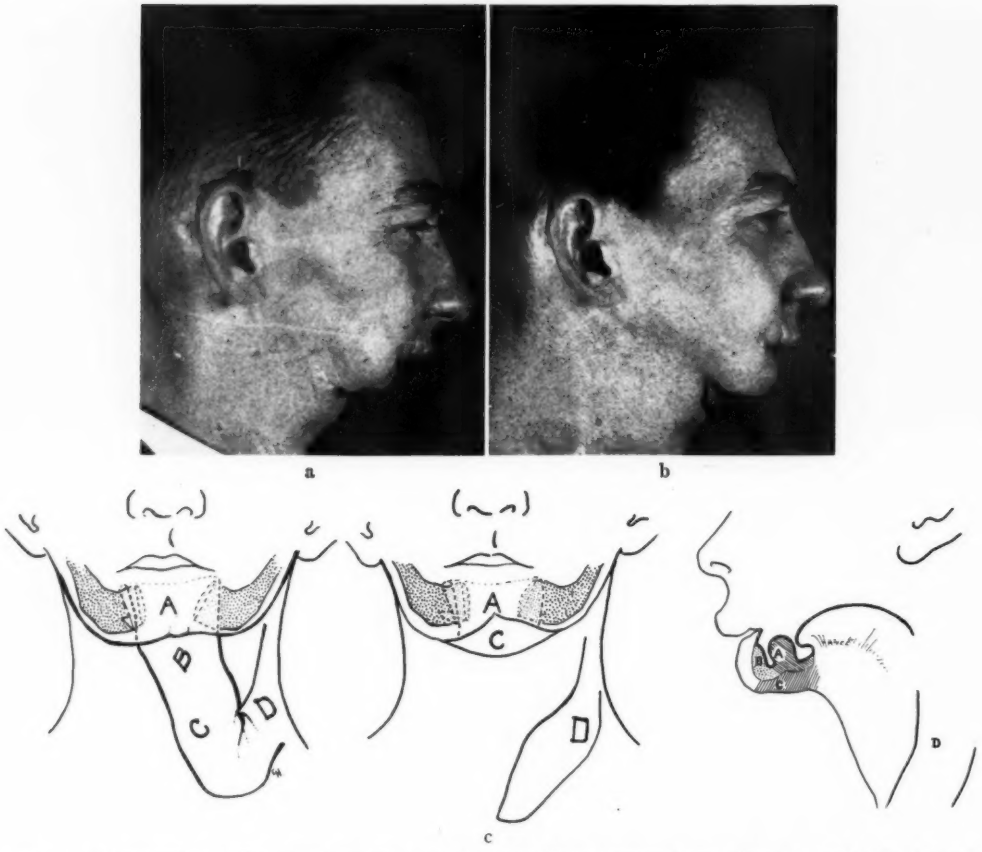


Fig. 8. a, Preoperative (taken on November 2, 1944), and, b, postoperative (taken on February 21, 1945) photographs of patient who had lost the anterior portion of his mandible from bicuspid to bicuspid area. There had also been loss of soft tissue. The scar tissue binding the anterior mandibular fragments was released. A neck chest flap was inserted to give added soft tissue. This same flap was used to line the buccal sulcus and cover lower border of chin. A bone graft has been inserted subsequently. c, Diagrammatic representation of source and use of flap tissue in b.

The site of resection of the mandible has usually been determined beforehand by studying the roentgenogram. If possible some portion of periosteum is left intact to bridge the gap. All bleeding is controlled. Where possible, mucosa is sutured so as to screen off the mouth from the neck portion of the wound, thus giving less contamination. The neck wound is closed accurately with a drain inserted.

Maintenance of jaw fragments. Wherever a resection is done some provision must be made to maintain the remaining fragments of the mandible in as near proper position as possible prior to bone graft repair (Table III). If there has been disarticulation in removal of the ramus, then only the anterior fragment must be considered, and in this case the simplest and best method of maintaining position is to wire the remaining teeth in occlusion until complete soft tissue healing has taken place. This same procedure may be the simplest also where there are teeth on both the anterior and posterior fragments. However, if the resection has been near the angle of the jaw so that the angle and ramus remain as the posterior segment, some means must be taken to maintain not only the space between fragments but also the posterior fragment in its proper position (Fig. 7). Various methods have been used to control the

a b c

Fig. 9. a, Preoperative (taken on November 2, 1942) and, b and c, postoperative (taken on December 20, 1943) photographs of a patient who had lost the entire left side of the mandible. The bony and cartilaginous portions of a rib were utilized. The bony portion was attached to the remaining mandible and the cartilaginous portion was inserted into the temporomandibular fossa. Note the increased fullness of the left side of the face in b. c, The dotted line indicates the position of the graft, the stippled area represents the bony portion of the graft while the clear area represents the cartilaginous portion of the graft.

posterior fragment (Table III). It is essential that this space retention be maintained until there is complete soft tissue healing. Otherwise as soft tissue healing occurs there will be progressive dislocation of the fragments by the pull of the new forming scar tissue and the various muscles. This dislocation will interfere with later repair by bone graft. This condition is especially common where mucosa has been removed and a granulating wound has been left inside the mouth to heal by secondary intention.

Reconstruction of the defect. Many patients have apparently been content to continue without having the defect in the mandible repaired. In some instances it has been possible for them to wear dentures. Unquestionably, the patient is more comfortable and his situation is more normal if a repair of the resected area of the mandible can be obtained with bony union. A number of methods may be employed but in general a free bone graft is the most desirable procedure.

In order to carry out the procedure of a free bone graft satisfactorily, certain things are necessary. The fragments of the mandible which remain must be free enough so that they can be not only placed but also maintained in their proper position during the time that the bone graft is healing in place (Fig. 7b). It is extremely important that the covering soft tissue be adequate in quality and amount to give good covering and nourishment to a bone graft. If the overlying tissue has been damaged to the point that it is scarred and tight, the graft is likely to be extruded. If it is necessary to dissect dense scar tissue from between the ends of the bone before they can be restored to their proper position then this must be done prior to the insertion of the bone graft to prevent mouth contamination. In certain instances it may even be necessary to apply additional soft tissue by means of flaps (Fig. 8) to replace scar or to supplement inadequate covering material which is present. This is done prior to the insertion of the bone graft. This is well illustrated in one patient (Fig. 8) who had lost two bone grafts because they were placed in dense scar tissue.

The bone graft may be either massive, using the half or full thickness of the rib or a section of the ileum, or it may be thin, as in the case of the osteoperiosteal graft taken from the tibia. This type of graft may be applied in several thicknesses. Regardless of the type of graft used, it is desirable to overlay the ends of the mandible with an inch or so of the bone graft where possible, making the bone graft two inches longer than the defect. In some instances the portion of the graft which overlaps the ends of the mandible may be thin while the portion between the ends is thicker. Sometimes a T-shaped graft may be employed, the thick arm of the T projecting in between the

ends of the mandible. In all instances, the bone grafts should be in as close contact with the mandible as possible and anchored to soft tissues or even to the bone itself with silk or fine tantalum wire sutures.

Where there has been a disarticulation of one side of the mandible, a rib graft containing cartilage and bone can be utilized. The cartilage end can be fitted into the temporomandibular fossa and the bony end attached to the remaining mandible (Fig. 9).

SUMMARY AND CONCLUSIONS

The ameloblastoma arises from the enamel organ during a particular phase of tooth development, namely, morphodifferentiation. Because the cells from which this tumor arises are not as yet differentiated into ameloblasts, the term preameloblastoma is more accurate.

This tumor is found most frequently near the angle of the mandible in young adults. Although the clinical history and roentgenographic findings are an aid, the final diagnosis depends upon microscopic examination.

It is slow growing and unless completely removed will continue to grow (rather than recur). The ameloblastoma seldom becomes truly malignant.

Curettement, cauterization with drugs, and radiation are inadequate therapeutic measures. The lesion should be (1) completely enucleated if unilocular, (2) cauterized by heat if not too large and multilocular, or (3) if extensive, resected, including a small amount of normal bone. These are the best methods of treatment because they give the greatest assurance of no tumor being left.

The surgical approach and procedure for various ameloblastomas and the necessary subsequent reconstruction surgery have been considered.

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BIOLOGIC INVESTIGATIONS OF A NEW ABSORBABLE SPONGE

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RECENT reports on fibrin foam (4,9) and oxidized cellulose (2,3,7) indicated that a material with the properties of a sponge that could be absorbed by the animal body might have utility in the general practice of surgery.

In a preliminary paper (1) there has been announced the preparation of a water-insoluble, gelatin-base sponge which fulfilled the requirements of an absorbable matrix. The purpose of this communication is to report the details of our investigations pertaining to the biologic uses and tissue responses to this new substance.

The physiologic absorption of catgut has been shown by Jenkins (5) to correlate with its enzymatic digestion *in vitro*. Gelatin sponge was found to digest *in vitro* in pepsin solution. The digest time was influenced by the mode of manufacture to the extent that some specimens digested in 10 minutes while undigested fragments of others persisted after 24 hours. There has been obtained evidence that the sponges which required the longest time to be brought into solution by pepsin *in vitro*, also demonstrated prolonged physiologic absorption in living tissues.

Most of the animal and all of the clinical investigations including a recent report in this journal (6) which have been made with gelatin sponge to date have employed material from lots which were standardized such that a 100 milligram cube of sponge was completely digested in 100 cubic centimeters of a 1 per cent solution (0.37 per cent HCl as solute) of U.S.P. pepsin at 37 degrees centigrade in 30 minutes or less.

Many different sized molds have been prepared from the foamed gelatin. The tough, porous, nonbrittle, sponge, after drying, was packaged and sterilized in the package by standard dry heat procedure. If autoclaved there resulted a complete loss of the desired physical properties. The final product could be handled with sterile technique and further cut to any desired shape and size (Fig. 1).

Pledgets were found to wet readily by dipping them in a solution and kneading vigorously in the fingers or sterile gloves for a few seconds. When the damp mass was returned to the solution it rapidly imbibed fluid and assumed its original shape and size. It was our practice to wet sponges in the particular solution which we wished to carry to an implant site.

An experiment designed primarily to ascertain if this slightly denatured protein material would be physiologically absorbed was conducted with 21 albino rats weighing about 300 grams. Sterile precautions were taken. The animals were anesthetized with ether, the outer surface of the left hind leg shaved and prepared with an antiseptic solution (mercresin). An incision about 25 millimeters long was made through cutaneous, subcutaneous, and fascial layers to expose the femoral muscles.

With a blunt instrument the muscle layers were divided and a dampened piece of gelatin sponge (6 by 8 by 8 mm., dry) was introduced. Well above the deep implant, a silk suture was taken to insure closure of the muscles and mark the site. Silk stitches were used to close the cutaneous wound.

Animals were killed each week and reopened for inspection. At 1 week the discolored sponges could be readily identified. At 2 weeks they had lost much of their original size and appearance. At 3 weeks only a small transparent gelatinous spot could be found at the implant sites. Nothing could be identified 30 days after implantation. In all 21 cases the wounds appeared clean and well healed, with no evidence of reactions that could be attributed to the sponge.

From the Research Laboratories of The Upjohn Company and (Dr. Prentice) the Prentice Clinical Laboratory.

Presented in part before the Committee on Surgery of the National Research Council, Washington, July 6, 1945. An abstract of this article is included in the 1945 Meeting-in-Print, Division of Medicinal Chemistry, of the American Chemical Society.

Fig. 1 Absorbable gelatin sponge. The illustration indicates how the material may be cut to any size or shape at the time of application.

The blood clotting enzyme, thrombin, has been recommended (8) as a useful hemostatic agent. Its clinical utility has been shown (4,9) to be enhanced if the thrombin is applied in an absorbable porous matrix that does not require removal at the time of wound closure. Such a procedure eliminates the danger of reinstating bleeding due to the need of withdrawing a dressing.

To gain information on the possible hemostatic properties of gelatin sponge when used in conjunction with thrombin, studies were made on the control of escaping blood from several artificially provoked bleeding points. In one investigation 6 rats were anesthetized with ether and the livers were exposed. In the left and right lobes of the liver, stab wounds were made of sufficient severity to produce a free flow. Small pieces of ordinary gauze were packed into the cuts in the left lobe. Into those on the right were inserted pledgets of gelatin sponge which had been wet in a thrombin solution of a potency of 500 units[1] per cubic centimeter. Before insertion, the wet sponges had been gently pressed in sterile gauze or towels so that they held as thrombin solution only about 25 per cent of their potential liquid engorging capacity.

Of the gauze filled wounds 5 either continued to bleed, or hemorrhage started again upon withdrawal of the pack. Only one indicated a control of the hemorrhage. Bleeding from the wounds packed with thrombin-damp gelatin sponge stopped in 2 minutes or less. These packs were not removed since removal would usually be contraindicated in clinical practice.

Often the sponge pledgets that served for hemostasis on the surface of a wound, since there was no overlying pressure, appeared bulky because of engorged blood and exudate. After a few moments, when the clotting was complete, pressure applied gently but firmly to such dressings caused them to lie as thin films. Because of the fibrin now precipitated in the interstices of the matrix, there was no further tendency to swell significantly.

Additional data were obtained by cleanly severing the tips of rats' tails and attempting to control the bleeding. Usually ordinary bandages did not stay the flow until considerable blood had been lost. Gelatin sponges damp with thrombin again demonstrated satisfactory control although the tails had to be adequately immobilized, or the wounds properly dressed, to avoid mechanical loss of the pledgets.

Another investigation was designed to study further the hemostatic qualities of gelatin sponge with thrombin and, by histologic examination, to evaluate more thoroughly the biologic absorbability of the sponge, as well as observe any cellular or tissue reaction it might provoke. Also, using the same animals and technique, the physiologic properties of fibrin foam and a starch sponge were investigated.

Twenty-eight 300 gram rats were anesthetized by intraperitoneal injection of 5 milligrams of cyclopentenylallylbarbituric acid

[1]Clotting activity was standardized at this time in our laboratory such that if 0.1 cubic centimeter of a solution clotted 0.5 cubic centimeter of specially oxalated bovine plasma in 15 seconds, that solution was considered to have a potency of 30 units per cubic centimeter.

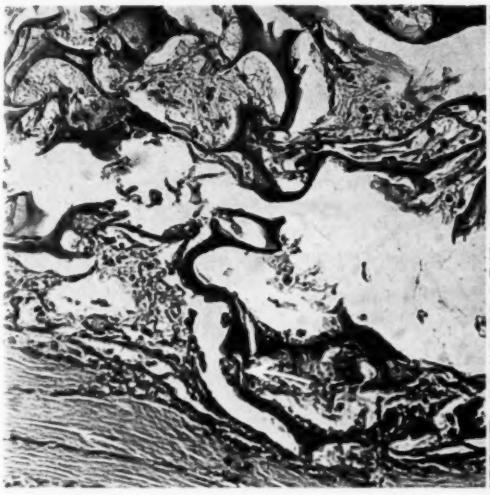

Fig. 2. Photomicrograph of gelatin sponge (arrow) that was embedded in rat muscle 5 days.

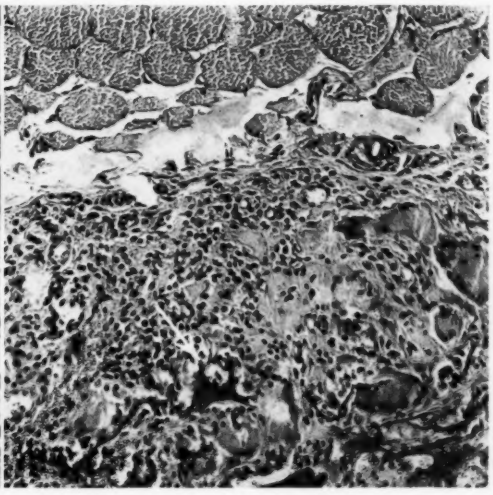

Fig. 3. Photomicrograph from a gelatin sponge (arrow) implant in rat muscle; 10 days postoperatively.

(cyclopal) per 100 grams of body weight. Both hind extremities were shaved and the areas painted with an antiseptic solution (mercresin).

Incisions about 25 millimeters long were made through the cutaneous layers in 4 different regions and the underlying muscles were exposed. All implanted pieces measured, dry, 5 by 8 by 8 millimeters. Those used in conjunction with thrombin were wet in a solution having a potency of 500 units per cubic centimeter.

In area A, the right leg, the muscles around the gastrocnemius were parted and a piece of fibrin foam, damp with thrombin, was introduced. Occasionally a saphenous vein was intentionally ruptured; the resulting hemorrhage was controlled by the fibrin foam-thrombin pack.

In area B, the right thigh, femoral muscles were separated and the pieces of starch sponge, moist with thrombin, implanted. The material made available to us at that time had very little cohesive strength in a wet condition, thus difficulty was experienced in making unbroken implants.

Into area C, the left leg, was inserted gelatin sponge damp with thrombin. Again a vein was often severed to create a bleeding which the gelatin sponge-thrombin combination readily arrested.

In area D, the left thigh, a piece of gelatin sponge wet with a solution of penicillin, which had a potency of 5000 Oxford units per cubic centimeter, was implanted.

Rats were killed at 5 day intervals from the 5th to the 100th postoperative day. The implant areas were visually inspected and specimens fixed in 10 per cent formalin solution. For histologic study the tissues were embedded in paraffin and stained with hematoxylin and eosin. Using this stain on unimplanted fragments, the gelatin sponge showed a mesh of purple fibers, the fibrin foam a pink and the starch sponge a shade of pink.

The considerable data accumulated will be abstracted to present only the pertinent information and thus avoid being voluminous.

Fibrin foam implants by the 10th postoperative day were dissected as yellowish lumps which when cut in two appeared as heavy walled fibrous capsules containing the original pledgets. These lumps grew progressively smaller the longer the rats were maintained; a little nodule was found in one out of two examined on the 100th postoperative day. Histologic examination of this specimen showed a remnant of foam with evidence of the sur-

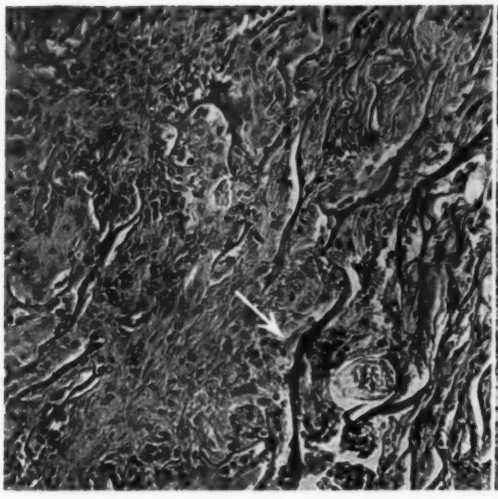

Fig. 4. Photomicrograph showing unabsorbed remnants of gelatin sponge (arrow) infiltrated by young connective tissue 20 days after implantation of a pledget into rat muscle.

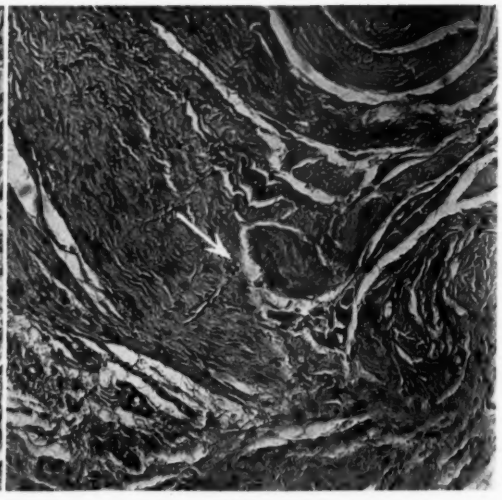

Fig. 5. Photomicrograph from a rat muscle area into which a piece of gelatin sponge had been implanted 30 days earlier. A little scar tissue identifies the site.

rounding fibroblastic capsule. Cellular and tissue reactions to fibrin foam were comparable to those to be illustrated for gelatin sponge.

Starch implants could not be identified by gross inspection after the 10th day. However, the prepared stained sections demonstrated pink colored fragments of starch through the 50th day. No significant tissue reaction to this material was observed but the 40 and 50 day specimens revealed an extraordinary cellular infiltration, largely of mononuclear phagocytes. The type of phagocyte that usually engulfs lipoids seemed to be attracted by this material invading and replacing it.

The physiologic responses to gelatin sponge whether introduced wet with thrombin or penicillin were the same.

Gelatin sponge implants were observed gradually to become gelatinous and transparent in appearance as they diminished in size. No tendency to encapsulate was noticed. By the 20th day only small transparent films could be found; these contained brown red discolored areas presumed to be hemoglobin residues from the enmeshed erythrocytes. Nothing was found by visual inspection after the 20th day and histologic identification of any unabsorbed material was doubtful after the 25th day.

No untoward tissue reactions were noted in the muscles subjected to gelatin sponge. There was some cellular reaction that was interpreted as being of no greater magnitude than usually arises during the resorption of a naturally occurring blood clot from an uncomplicated wound.

Histologic sections of a gelatin implant specimen at the 5th postoperative day (Fig. 2) showed the meshes of the sponge lying close to muscle tissue with very little evidence of cellular reaction. At 10 days (Fig. 3) sponge material was seen as were leucocytes and giant cells. At the 20th day sponge remnants were found along with infiltration of young connective tissue. By the 30th postoperative day (Fig. 5) no sponge was identified by histologic staining; the cellular reaction was subsiding. In our experience cellular response appeared to become maximal in 10 to 25 days, then recede.

SUMMARY

A water-insoluable, gelatin-base sponge has been prepared. This matrix was found to be digested *in vitro* in pepsin solution and *in vivo* to be physiologically absorbed.

In conjunction with thrombin, gelatin sponge has been shown to act as a hemostatic agent for hemorrhages that were experimentally provoked in animals.

In additional studies implants of fibrin foam, starch sponge, and gelatin sponge were enclosed in rat muscle areas. At stated intervals the operative sites were reopened, visually examined, and specimens fixed for histologic study.

The fibrin foam implants were not completely absorbed, as indicated by histologic evidence, by the 100th postoperative day. There was evidence of fibrous encapsulation of this material. No significant tissue reaction was observed. Cellular response was comparable to that observed in the gelatin sponge implants.

No starch sponge could be visually identified after the 10th day, but histologic evidence indicated unabsorbed fragments through the 50th day. This substance excited considerable cellular response, particularly of the mononuclear phagocytes.

Gelatin sponges were soaked in penicillin solution and inserted in wounds. These absorbed as readily as other gelatin sponge implants, with similar physiologic responses.

Thrombin-damp gelatin implants were absorbed by the 30th postoperative day as illustrated by the histologic data. There appeared to be no tendency for this material to encapsulate. No tissue reaction was observed. The gelatin sponge pledgets provoked a cellular infiltration which was considered to be no greater than occurs upon the resorption of an ordinary blood clot. The cellular reactions were found in these experiments to become maximal in 10 to 25 days and then recede.

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EDITORIAL

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THE VALUE OF GASTROSCOPY IN THE DIFFERENTIAL DIAGNOSIS OF ULCER AND CARCINOMA

IN A recent editorial[1] on "The Ulcer Carcinoma Problem of the Stomach," Bisgard stated that "Gastroscopy is of no help because it provides merely the observer's visual impression which at best lacks the precision necessary in dealing with carcinoma." It seems to me that this statement is not quite fair to the gastroscopist because, although he may make some mistakes, he is sometimes able to give quite positive evidence that an ulcerating lesion of the stomach is malignant. When, for example, he sees a rather large ulcer with ragged nodular margins and a dirty base over which peristaltic waves do not pass, he can be fairly certain that he is dealing with a malignant ulcer. On the other hand, when he sees a comparatively small ulcer with sharp margins and a clean base with no surrounding induration and no interference with the peristaltic wave, he will usually be correct in believing that the ulcer is benign.

Unfortunately, as in the case of most other diagnostic procedures, it must be admitted that such evidence cannot be considered 100 per cent correct, but the gastroscopic picture is of value when added to the x-ray examination and the clinical data. In my opinion, a more accurate diagnosis can be obtained in the gastric ulcer carcinoma problem when all methods of examination are used in a given case, than when reliance is placed on incomplete data. Gastroscopic examination supplements x-ray examination; it does not in any sense compete with it. Reliance can be placed upon gastroscopic examination only when the method is carried out by an experienced gastroscopist who knows the limitations of the method, the relative blind areas in the stomach, and the proper interpretation of his observations. If gastroscopy, x-ray examination, and the clinical data all point to a benign lesion, we believe it is safe to keep the patient in bed in the hospital for a period of three weeks on a careful medical regimen, then reexamine by x-ray and by gastroscopy, and reevaluate the situation. If there is any question of carcinoma, the patient should be explored surgically. A fairly safe rule in dealing with gastric ulcer is to consider it malignant until proved otherwise, but I do not believe that it is fair to say that gastroscopy is of no help whatsoever in the ulcer carcinoma problem.

In a recent lecture Benedict[2] studied 245 proved cases of gastric pathology in an at-

[1]Bisgard, J. D. Editorial. Surg. Gyn. Obst., 1944, 79: 673.

[2]Benedict, E. B. Pancoast Memorial Lecture. Correlation of Gastroscopic, X-ray and Pathological Findings in Diseases of the Stomach—An Analysis of 245 Proven Cases. Philadelphia Roentgen Ray Society November 2, 1944. (In press.)

tempt to correlate the gastroscopic, x-ray, and pathological findings. An analysis was made of 125 cases of proved carcinoma of the stomach in which it was shown that x-ray and gastroscopic examination were equally good in 67 cases, equally doubtful in 3 cases, the radiologist more accurate or more helpful in 32 cases, and the gastroscopist more accurate or more helpful in 20 cases. When the lesion was equally accessible to both methods of examination, the analysis seemed to indicate the relative superiority of gastroscopy over radiology in differentiating benign from malignant gastric ulcers. In the same report, 50 cases of proved benign gastric ulcer were also analyzed, and in 16 of these x-ray and gastroscopy were equally correct, in 9 cases equally doubtful, in 21 cases x-ray was superior to gastroscopy, and in only 4 cases gastroscopy was superior to x-ray. In both the carcinoma and the ulcer cases, gastroscopic failures were due largely to mechanical difficulties, which accounted for 25 of the 32 cases of x-ray superiority in the carcinoma group and for 17 of the 21 cases of x-ray superiority in the ulcer group.

In conclusion, I believe that gastroscopy is of value in the ulcer carcinoma problem and that the most accurate diagnostic results are obtained when all methods of study are used co-operatively. EDWARD B. BENEDICT.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

FIVE concise and well presented articles on the diagnosis and treatment of spina bifida, cranium bifidum, and other related malformations of the central nervous system by Franc D. Ingraham and his associates reprinted from the *New England Journal of Medicine* are presented under the title of *Spina Bifida and Cranium Bifidum*.[1] An extensive and comprehensive bibliography of 129 pages covering the literature of spina bifida from 1556 to 1943 is included.

The first article is an analytical survey of 462 cases of spina bifida and 84 cases of cranium bifidum observed at the Boston Children's Hospital during the past 20 years. It emphasizes the fact that associated anomalies such as hydrocephalus, club foot, bone and central nervous system maldevelopments are very common and do not constitute a contraindication to surgical treatment if they are not progressive. The myelomeningoceles constitute the largest group. The various types of lesions are classified and their relation to sex, age, site, and symptoms are presented in clear tables. The majority of the spinal defects are found in the lumbosacral region and of the cranial defects in the occipital bone. The operative indications and contraindications are discussed and it is evident that the authors do not consider neurologic disabilities as a contraindication to surgical treatment. Thirty-four per cent of the patients with encephalocele and 30 per cent with spina bifida are found to lead a relatively normal life after operation.

The surgical treatment of myelomeningoceles and encephaloceles is presented in the second article. Although uncomplicated cervicodorsal meningoceles and encephaloceles may be operated upon successfully in the first days or weeks after birth, the authors recommend a delay in surgical intervention as the wisest general course to pursue. A careful evaluation of the individual problems involved is always necessary and requires time and patience. The essential features at operation are a tight closure of the dural sac and a firm closure of the subcutaneous tissues and the skin. The authors stress the importance of meticulous postoperative and nursing care and present adequate measures to stop the development of postoperative cerebrospinal fluid fistulas and regulate the cerebrospinal fluid dynamics.

An analysis of 65 cases of spina bifida occulta is presented in the third article. This defect is frequently associated with other maldevelopments, but produces symptoms in only a very small group of individuals. Early operation is advised for patients who present a progression of symptoms especially in the lower extremities. In 22 cases laminectomy was performed and in 12 of them a lipoma was found within the spinal canal. The authors state that "it is important that patients who are developing equinus or cavus deformities be operated on early, because such deformities once present cannot be expected to disappear following operation." However, they fail to mention if an early laminectomy or an exploration stopped the development of such deformities.

The fourth article deals with an unusual case of nasopharyngeal encephalocele due to a defect in the cribriform plate and with its successful surgical treatment.

The Arnold-Chiari malformation is discussed in the fifth article which is based upon the study of 20 cases. It is interesting to note that all of them had a myelomeningocele and a hydrocephalus and that microgyria and craniolacunia were often present. Advanced hydrocephalus and extensive paralysis constitute a contraindication to surgical treatment. However, it remains difficult to diagnose this condition preoperatively.

This book contains well chosen illustrations and brings understanding and clarity in this rather neglected and unduly pessimistic field of surgery.

GEORGE PERRET.

THE monograph *La radiologia en el estudio de la vesicular biliar*[1] is a publication from the Radiodiagnostic Section of the Institute of Radiology of the Faculty of Medicine of Montevideo, under the direction of Professor Pedro A. Barcia.

The book deals with all the roentgen methods of gall-bladder examination, including cholecystography. The various phases of the direct x-ray examination of the gall-bladder region without the aid of opaque device is described in detail. Naturally cholecystography is discussed at length. Because of the frequency of hydatid disease in Uruguay, the authors have much experience in the differential diagnosis of hydatid cysts of the liver, which in some phases resemble gall-bladder shadows. The undated work consitutes an excellent summary of the present knowledge of the gall-bladder study by the x-ray.

JAMES T. CASE.

[1] SPINA BIFIDA AND CRANIUM BIFIDUM. Papers reprinted from the *New England Journal of Medicine* with the addition of a comprehensive bibliography. By Franc D. Ingraham, M.D., and collaborators. The Children's Hospital, Boston. Cambridge, Mass.: Harvard University Press, 1943, 1944.

[1] LA RADIOLOGIA EN EL ESTUDIO DE LA VESICULAR BILIAR (Radiology in the Study of the Gallbladder). By Pedro A. Barcia, and Agustin Gorlero Armas. Buenos Aires: Librería y Editorial "El Ateneo," 1945.